‘Paediatric Bipolar Disorder’:

Why did it occur, the iatrogenic consequences, and the implications for medical ethics and psychiatric nosology

by

Peter I. H. Parry

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ABSTRACT

This doctoral thesis examines a major controversy in the field of child psychiatry: the diagnosis and treatment of bipolar disorder among prepubertal children. Part I presents the development of 'paediatric bipolar disorder' (PBD), which became a frequent diagnosis in the US. Part II contains three new studies on critical areas of PBD research. Part III discusses the implications of the PBD phenomenon for psychiatric ethics and nosology.

The PBD controversy began in the mid-1990s when US child psychiatric researchers from two prestigious universities hypothesised that bipolar disorder frequently presented with atypical mania among prepubertal children. PBD was rapidly translated into clinical practice in the US, as probably over a million children and young adolescents were diagnosed and treated for PBD over the next two decades. The most contentious aspect was the off-label prescription of medications, typically reserved for adults with bipolar disorder, including second-generation antipsychotics.

Part I describes how the media, restrictive health insurance, parent support groups, pharmaceutical industry funding of research, continuing medical education, direct to consumer advertising, and the dominant biomedical paradigm within US psychiatry combined to rapidly translate the PBD hypothesis from academia into clinical practice.

My original contribution to knowledge enfolds the published studies that form the three chapters of Part II. The methodology for Part II is a re-examination of the peer-reviewed research. The first study examined a highly cited meta-analysis that claimed that bipolar disorder is prevalent in community epidemiological studies of children and adolescents. This crucial claim was used to argue that the high diagnostic rates of PBD in the US were consistent with the high community prevalence, and PBD was underdiagnosed internationally. However, re-examination of the individual studies found bipolar disorder to be exceedingly rare before mid-adolescence. The published findings precipitated a nine-article debate in a later issue of the journal, the largest debate on the PBD topic (Chapter 4.8.8.2).

The second study examined whether academic psychiatrists outside the US supported the PBD hypothesis of atypical prepubertal mania. Using bibliometric methods, the study found

that authors from a few US academic centres wrote most of the articles supporting PBD, but the majority of non-US authors were sceptical of the PBD hypothesis.

The third study examined whether studies of PBD investigated alternative causes of childhood mood lability such as attachment disorganisation, maltreatment and trauma. This bibliometric analysis found that very few PBD studies investigated these contextual factors. This is a significant oversight; given these factors are proximal and frequent causes of childhood mood lability.

Finally, Part III – the Discussion – explores the implications of the PBD phenomenon, and the three new studies. The findings suggest that PBD was prematurely translated into clinical practice in the US, despite lacunae in the research. The translation was not firmly based on science but was related to unique aspects of the US health system and sociocultural dynamics involving the influence of the pharmaceutical industry. The Discussion outlines the iatrogenic consequences of the rise of PBD, and the implications for medical ethics and psychiatric nosology and training.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Dr Peter I H Parry

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Thirteen years ago, I set out to understand the phenomenon of 'paediatric bipolar disorder'. On the basis of my emerging concerns about this apparent new diagnosis, and the increasing use of atypical antipsychotics among children and adolescents, I wanted to promote discussion and debate about this new diagnosis from the US, before child psychiatrists and paediatricians in Australia and New Zealand possibly adopted it. This in turn led to participation in the international academic debate about this controversial diagnosis, and eventually the decision to combine the critical aspects of the discussion into a thesis.

In undertaking this thesis, formally commenced in March 2009, my original plan was to chronicle the history of PBD, identify some of the factors that led to an historic shift in US child psychiatric practice, and discuss the implications of this.

It has been a long journey, and I have met many wonderful colleagues along the way who have been of great assistance in understanding the PBD phenomenon. It has been a real inspiration to join with several of them as collaborators in conferences, and co-authors of published papers that contributed to the academic debate on this controversial topic.

Firstly, I owe immense gratitude to my supervisors, Tara Brabazon and Paul Ward, whose expertise in higher degree research, culture studies and medical sociology have helped me synthesise such a broad topic. I have also had the privilege of working with two external supervisors, who are among the world's leading scholars in psychopharmacology, David Healy and Jon Jureidini. They have campaigned to make medicines safer for all, and their work has brought to wider international attention, the interactions between medicine and pharmaceutical company marketing.

I thank my colleagues Stephen Allison and Tarun Bastiampillai, who have been a source of much support as well as co-authors on a number of articles. I must also thank and honour the work of the many US child psychiatrist colleagues who I have met and collaborated with on this journey, particularly Ed Levin, Gordon Harper, Jennifer Harris, Stuart Kaplan, Glen Elliott, Mary Burke, Stuart Bair, Jess Shatkin, James Grubbs, Uri Cohen, Joshua Feder and Gabrielle Carlson, as well as US paediatrician Larry Diller. I would like to thank my co-author on the internal industry documents study, psychologist Glen Spielmans, and US adult psychiatrists,

(the late) J Mickey Nardo, Daria Inbar, Daniel Carlat, Nicholas Rosenlicht and Helena Hansen, as well as Canadian child psychiatrist Normand Carrey and British child psychiatrist and co-author Louise Richards. I would particularly like to thank and honour an eloquent young American who gave the story of his PBD diagnosis, referred to herein as 'Adam'. Many Australasian colleagues have supported my work: to name just a few, John Callary, Paul Dignam, Michael Berk, Soumya Basu, Melissa Raven, Stephen Stathis, and two personal mentors: Graham Martin and Barry Nurcombe. I also offer deep gratitude to Brenda Jericho, and Tristan Badger for editorial assistance and proof reading. I also offer gratitude to Madeleine Parry for editorial assistance and IT support in the final stages. I thank Miltos Antoniades of achievepresentations.com for assistance with the pie chart figures in Chapter 7 and the Medical Illustration and Media department of Flinders Medical Centre for assistance with the pie chart figures in Chapter 8.

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PROLOGUE

Motivation and epistemological basis for this thesis

Historically established perspective on bipolar disorder and the emergence of the hypothesised alternative: age range and symptomatology

This doctoral research concerns what an editorial in the *American Journal of Psychiatry* called a "notoriously controversial" topic, that being: "whether [bipolar disorder] can be diagnosed in pre-pubertal children at all" (Ghaemi & Martin 2007, p. 185). The "notoriously controversial" nature of the subject matter warrants this prologue to explain the perspective I have taken as both a researcher presenting this doctoral thesis, but also as a published protagonist in the debate on the topic.

There is a historically and globally established position, dating at least from the time of Emil Kraepelin's (1921) seminal work *Manic-Depressive Insanity and Paranoia*, that mania almost invariably first presents from mid/late adolescence into adulthood (Chapter 2.1), and that earlier onset cases are exceedingly rare. This view has been termed the 'conservative' perspective (Carlson & Klein, 2014; Chapter 4.8.2.35). However, from the mid-1990s, an alternative view was presented in several US-based child psychiatric research centres, that mania commonly presents from early pre-pubertal childhood (Chapter 3.3), albeit with atypical symptomatology. The atypical symptoms ranged from ultradian (several times per day) mood cycling between elevated and depressed mood (Geller et al. 1995) to purely chronically irritable mood without elevation (Wozniak, Biederman, Kiely, et al., 1995; Chapter 3.2). This alternate perspective is what can be termed the 'paediatric bipolar disorder' (PBD) hypothesis. While aspects of this hypothesis had been suggested at times over the previous century, there were few adherents. However, during the mid-1990s the PBD hypothesis was rapidly adopted as the prominent view in a number of US child psychiatric academic departments. It later spread to a few non-US centres, notably in Brazil, Spain, Italy, Turkey and South Korea (Chapter 7). Carlson and Klein (2014) termed this the 'liberal' perspective. The PBD hypothesis therefore deviated markedly from the historically accepted definitions of bipolar disorder both in terms of age of onset and symptomatology. In fact recently, a quarter century after the seminal PBD articles of Geller et al. (1995) and Wozniak, Biederman and

Kiely et al. (1995), the PBD hypothesis remains so controversial that "Geller-Wozniak Syndrome" has been suggested as an alternative name for these types of phenomenology that does not carry "erroneous assumptions about aetiology, associations, treatment and prognosis" (Hazell, P 2019, p.1).

In writing a thesis on a highly controversial topic, it is necessary to be transparent and state my view on the matter, to 'nail my colours to the mast' so to speak. As a child and adolescent psychiatrist trained and practising in Australia, as well as for a time in the UK, like the majority of my colleagues, I have adhered to the historically and geographically dominant 'conservative' view. This view has prevailed in both Australasian and British child psychiatry.

Therefore, it is important to be clear about the epistemological basis for this thesis. On what foundation do I claim that the long-held conservative view is ontologically accurate? Am I simply following the views of my Australasian and British peers? Further, how can I argue what I believe to be true in this controversy, when the majority of the published literature on PBD in its 'Geller-Wozniak syndrome' version is in favour of the proposition of pre-pubertal onset of mania/bipolar disorder? The debate on PBD raises challenges for the epistemology of a 'social science' field like child psychiatry. What are the solid findings that the fields of psychiatry, developmental psychology and descriptive psychopathology and phenomenology rest upon?

The PBD hypothesis has generated much data and, in turn, this has led to many peer-reviewed articles supportive of it. However, data supporting the PBD hypothesis has been based on the somewhat circular logic of re-setting criteria according to the PBD hypothesis that then generates the research data. Journals then published the research, in part because it contained quantitative data. This may have been particularly likely where editors and reviewers may have been favourable to the PBD hypothesis. In contrast, anecdotally at least, it proved difficult to publish articles sceptical of the PBD hypothesis because such articles by necessity lacked research data on a postulated disorder that conservative perspective authors did not believe existed.

Thus, the majority of the published academic literature with respect to the PBD hypothesis has a majority liberal pro-PBD hypothesis perspective (Chapter 7). The smaller academic

literature on PBD that supports the conservative view in the early years of the PBD epidemic could only take a sceptical opinion-based perspective and was often lacking in quantitative data. There was sceptical perspective quantitative data from a couple of surveys (Meyer, TD, Kossmann-Bohm & Schlottke 2004; Parry, Furber & Allison 2009a), and a trans-Atlantic comparison of US and British child psychiatrists' diagnosing patterns (Dubicka et al. 2008). However, proponents of PBD described this as still opinion-based (Youngstrom et al. 2012).

In more recent years, the data from follow-up of 'broad phenotype' (predominantly irritable mood) PBD cohorts indicated they did not progress to bipolar disorder in young adulthood (Stringaris et al. 2009). Additionally, longitudinal high-risk offspring studies revealed five out of six of such studies found no cases of hypomania/mania under age 15 (Duffy, Malhi & Grof 2017), and international comparisons of clinical diagnostic rates of bipolar disorder in the child and adolescent population (Clacey, Goldacre & James 2015) indicated stark quantitative differences in diagnosing practices between the US and other countries. This later data is helping to disprove the PBD hypothesis and coincides with a waning of pro-PBD literature, but it is an interesting point that it took about two decades to muster quantitative data to counter the quantitative data produced by a redefinition of diagnostic criteria created on the basis of opinion.

Editors of journals appear to place greater faith in quantitative research than qualitative research or opinion-based critiques. Generally, in the hard sciences and also the social sciences this may be justified. However, where a subject is controversial, a case can be made that countervailing arguments that critique the methodologies that led to certain quantitative data, need to be aired in the literature. In the PBD literature, various journals appear to have been more open to publishing sceptical articles than others. It is the case that I am an author or co-author for a significant number of the sceptical articles on PBD (Appendix A).

My co-authors and I experienced this valuing of quantitative research data over clinical opinion in a response to a letter (Chapter 4.8.2.16) we submitted to *Archives of General Psychiatry* where we cited the sceptical positions represented by the German and Australian and New Zealand surveys of child psychiatrists, as well as the British National Institute for Health and Clinical Excellence (NICE) expert committee on bipolar disorder. The reply from the journal editorial board dismissed the German and Australia and New Zealand surveys as

being of low evidentiary status. This is despite the German and Australia and New Zealand surveys cumulatively representing over 7,000 years of child and adolescent psychiatrist clinical experience. Therefore, this thesis also raises questions about how can the academic literature balance quantitative with qualitative data driven research, how can the quality of 'evidence-based' research be best evaluated, and what place does clinical experience and opinion hold in setting standards, clinical guidelines, the academic discourse and training curricula for psychiatry?

To present the epistemological underpinnings of this thesis, this prologue extends beyond the published academic literature to include anecdotal and personal accounts of aspects of the controversy surrounding the PBD hypothesis. This will allow the reader to understand the epistemological basis for the 'conservative' (Carlson & Klein, 2014) perspective taken in:

1. writing a narrative history of the PBD phenomenon (Part I);
2. investigating systematically certain aspects of the PBD literature (Part II); and
3. discussing and arriving at possible conclusions as to how and why the PBD phenomenon occurred (Part III).

Personal clinical experience and introduction to the PBD hypothesis

In my clinical experience, the youngest case of mania that I have ever seen was that of a 14-year-old, though I have been aware of Australian colleagues on a couple of rare occasions treating 12-year-olds and one 8-year-old. The 14-year-old was normally not keen on school and came from a non-religious family; however, one day he eagerly attended school in a euphoric mood after a sleepless night preparing a speech for assembly that proclaimed he was the messiah. He required inpatient treatment and responded to lithium and antipsychotic medication and resumed his premorbid non-religious views. The phenomenology was typical of the cases of mania, and the milder cases of hypomania, as well as some mixed mood episodes, that I had observed during my medical school psychiatry attachment, general medical practice in the 1980s and my psychiatry training at a large psychiatric hospital in South Australia in the early 1990s.

Generally, however, in my clinical experience, the age of onset for mania was 16- or 17-years-old amongst the under-18 age group treated by the clinics I have worked for over the past 25

years. I witnessed several such cases of mania in older adolescents, particularly when I was working on the sole South Australian child and adolescent inpatient unit, Boylan Ward at the Women's and Children's Hospital, North Adelaide, from 1998 to 2003 and later as medical director of the mental health services at the Queensland Children's Hospital from 2014 to 2016. It was during that first inpatient role that colleagues pointed me to a copy of *TIME Magazine* with the cover dominated by a portrait of a pre-pubertal boy and the headline: "Inside the volatile world of the YOUNG AND BIPOLAR: Why are so many kids being diagnosed with the disorder once known as manic-depression?" (Kluger & Song 2002). We were perplexed by the article: none of our colleagues had seen a pre-pubertal case of mania, yet this article reported several US child psychiatrists indicating the illness commonly began in early childhood and even infancy. At the time, we deemed the article must be some kind of aberration.

The topic of PBD did not again make a conscious impression upon me until 2005 when I was working as a locum in the child and adolescent mental health service in Bangor, North Wales, UK. The local professor of psychiatry, David Healy, drew my attention to this new disorder, PBD, in the US. Healy, who also later became a supervisor for this thesis, is a renowned historian of psychiatry. I was shocked but still did not appreciate the magnitude of the issue. In 2006, I helped organise grand rounds for Professor Healy's visit to Australia and found his presentation and article on PBD disturbing (Healy 2006). He reported thousands of US children were being diagnosed, some in toddlerhood. Healy showed slides from the book *Brandon and the Bipolar Bear* (Anglada 2004). I had a visceral reaction to the book. Having been a keen reader of bedtime stories to my own children, I was horrified by what I saw as extreme medicalisation of childhood behaviour issues or even of normal developmental temper tantrums and the inherent oppositional stances that accompany individuation stages.

These diagnostic and therapeutic practices in the US concerning PBD were foreign to all my training and clinical experience in child and adolescent psychiatry since entering the sub-speciality in 1995. I had participated in several conferences in both Australia and the UK, and also completed a study tour of a dozen UK paediatric psychiatric inpatient units but had somehow heard almost nothing about what had become the most common diagnosis in US preadolescent inpatient units (Blader & Carlson 2007). In discussion with many Australian,

New Zealander and British child psychiatrist colleagues I found that my lack of awareness of PBD to that time was the norm.

This sudden awareness of PBD and the surprisingly (for me) large, almost solely US based, psychiatric literature on PBD caused me to question my own training and clinical practice. Were the US academics who defined and treated PBD correct? Were I and my colleagues in the UK and Australasia incorrect in not making a diagnosis of bipolar disorder in children and teenagers exhibiting symptoms of either ultradian mood cycling or chronic irritability? It simply was not possible to match the PBD literature to my own clinical experience, and I therefore remained sceptical of the PBD hypothesis and continued to adhere to my Australian training and clinical practice.

My experience of involvement in the PBD debate

In 2007, with assistance from Stephen Allison, the head child psychiatrist at Flinders Medical Centre where I was working at the time, we surveyed members of the Faculty of Child and Adolescent Psychiatry of the Royal Australian and New Zealand College of Psychiatrists (FCAP of the RANZCP) with the full support of the RANZCP headquarters in Melbourne. Members of the FCAP of the RANZCP were at that time becoming aware of the PBD hypothesis and there was concern about Australian paediatricians diagnosing cases. There was a 60% response rate as 199 Australian and New Zealand child psychiatrists completed the survey. The results were published in the journal *Child and Adolescent Mental Health* (Parry, Furber & Allison 2009a; Appendix A4) and in the *FCAP eBulletin* (Parry 2008a; Appendix A5). Following this I became an active participant in the debate about PBD, first nationally and later internationally. This was not something I had planned for my career in child psychiatry, but I felt it an important issue to address. Along the way I came to meet many colleagues, particularly those from the US, some of a pro-PBD viewpoint, but with the majority sharing my classical conservative perspective. Some, particularly Ed Levin from Berkeley, California, have become dear friends and we have published articles together (Levin & Parry 2011; Appendix A15; Parry & Levin 2012; Appendix A18) and co-presented at conferences in the PBD debate (Parry et al. 2009; Appendix A8; Levin et al. 2013). With others, we have discussed PBD and even co-authored articles, all online. I have sought to thank as many as I can remember in the Acknowledgements.

In particular I was motivated by a young man 'Adam' (name changed to maintain confidentiality) living in the US, whose story I heard via email after we discussed PBD on a health politics forum in 2008. This was expanded upon in a published article (Parry 2014a; Appendix A26) where I give space to 'Adam' to tell his personal experience of being diagnosed with PBD, and I reference 'Adam's views' in Chapter 9. We felt if we could sway the debate in the US, it might be helpful to many like him. My wife, Anja Kriegeskotten, and I later met and dined with him on a visit to the US. Also a child psychiatrist, she found 'Adam's' story genuine and compelling. His gratitude for my work was touching and helped encourage me to believe that pursuing this topic was important, perhaps more so than studies in the therapeutic areas of child psychiatry I previously wished to pursue.

On the same health politics forum (the now defunct www.furiousseasons.com blog) internal pharmaceutical industry documents were posted that showed at least some companies engaged in diagnosis promotion to increase sales, particularly the diagnosis of bipolar disorder and 'juvenile bipolar disorder' (JBD). My response to this was to publish and speak about such documents. The article "From evidence-based medicine to marketing-based medicine: evidence from internal industry documents" was co-authored with US psychologist Glen Spielmans (Spielmans & Parry 2010; Appendices A10, A11). The feedback from the annual lecture I give on these documents to child psychiatry trainees in Brisbane is positive and reported as "eye-opening". The information in such documents has a direct bearing on the PBD topic as is discussed in Chapters 4.2 and 9.4.5. These documents and other literature show that the role of the pharmaceutical industry in marketing new diagnoses and widened categories of diagnoses cannot be stressed highly enough. It is a practice that has been termed 'disease mongering' (Moynihan, Heath & Henry 2002).

When a group of Australian academics started seriously exploring the PBD hypothesis (Cahill, Hanstock, et al., 2007) and the journal of the RANZCP, *Australian and New Zealand Journal of Psychiatry (ANZJP),* published a guest editorial by two US PBD researchers (Mao & Findling, 2007), fifteen South Australian child psychiatrists submitted a letter to the *ANZJP* noting that PBD "is a controversial diagnosis" (Parry et al. 2008; Appendix A1) and "children will run the risk of serious side-effects" from pharmacotherapy before diagnosis of bipolar disorder is clear (p. 91). At the time, we were concerned about Australia importing the epidemic.

I recall a conversation also in 2007 with a senior Australian child & adolescent psychiatrist colleague, Dr Nick Kowalenko (later chair of the FCAP of the RANZCP) about the contradictory nature of the American Academy of Child & Adolescent Psychiatry (AACAP) official practice parameter guidelines on bipolar disorder (McClellan et al. 2007). The guidelines reflected diametrically opposing views within American child and adolescent psychiatry and we could not imagine our own faculty needing to produce such a conflictual document. The FCAP of RANZCP survey and the response to my participation in debates and presentations at annual meetings of both the FCAP of the RANZCP in 2007 (Parry 2007) and 2008 (Parry, 2008a) and the RANZCP full Congress in 2008 (Parry, 2008b) made it clear that my sceptical perspective was shared by the overwhelming majority of my Australian and New Zealand colleagues.

Following the debate at the 2007 FCAP of the RANZCP meeting in Hobart, I was approached by two US child psychiatrists, both working as locums in New Zealand at the time. James Grubbs, child psychiatrist from Texas, said that in over 30 years he had only seen one prepubertal case, an 8-year-old girl, with classic symptoms of mania. This girl had an extreme genetic loading according to Grubbs: both her parents and all four grandparents had bipolar-I disorder. He told me he had trained with several leading PBD researchers and, in his opinion, they had simply shifted the diagnostic goal-posts without a robust scientific rationale (J. Grubbs, 2007, conversation, 11 October). The other US colleague, Craig Carpenter from Ohio, said he found my presentation very interesting because he had trained in one of the leading pro-PBD departments in the US, where the "number one question was whether the child you are seeing has bipolar disorder or not" (C. Carpenter, 2007, conversation, 11 October). He said during his training he had diagnosed at least six new cases of children and young adolescents. He also noted that parents in the US often came to appointments expecting their child to be diagnosed with bipolar disorder, and reflected on the fact that after six months working in a New Zealand Child and Adolescent Mental Health Service community clinic not one family had raised the prospect of a bipolar diagnosis and neither had he once considered it. Both Dr Grubbs and Dr Carpenter encouraged me to continue my exploration into this topic and write articles that their colleagues in the US might read. At this early stage it was still somewhat mystifying to me as to why the US had largely succumbed to a PBD epidemic. I decided to formalise my exploration of this topic and my participation in the debate about PBD into a doctoral thesis.

During 2009, I attended the AACAP annual meeting in Honolulu, Hawaii, to give a poster presentation of the findings of the FCAP of the RANZCP survey of Australasian child psychiatrists' views on PBD (Parry, Furber & Allison 2009b; Appendix A6). The poster attracted considerable interest and discussion with mainly US child psychiatrists that continued beyond the poster session time period. I was informed of how the US health care system encourages 'diagnostic upcoding' to more severe disorders such as bipolar disorder, so that the cost of the appointment can be reimbursed when otherwise it may not be, and also how larger health care employers pressured psychiatrists into more lucrative brief 'med-check' appointments that restricted time for inquiry into causative factors for children's symptoms, such as trauma and attachment issues. These discussions highlighted the impact of the systemic pressures of a health system on diagnostic practice, and how the basic tasks of exploring and assessing the contextual factors impacting on children's symptoms could be neglected.

I later explored this further and reviewed the PBD literature for reference to (or rather lack of reference to) attachment and developmental trauma factors (see Chapter 8). This literature review juxtaposed the research in developmental neuropsychology about the importance of attachment and developmental trauma with the descriptive psychiatry-symptom check-list approach utilised in much of the PBD research. To my mind it exposed an important disconnect and siloing or compartmentalising of key bodies of knowledge. I presented preliminary findings early in my thesis at an International Society for Affective Disorders conference in Brisbane (Parry 2009a). Professor Michael Berk of Deakin University, president at the time of the International Society for Bipolar Disorders (ISBD), was attending and encouraged me to continue with this research and we co-authored an article (Dignam, Parry & Berk 2010; Appendix A12), and I later presented a grand round on the PBD controversy to his department in Geelong. The response to these presentations was encouraging, and I further presented an updated literature review at the International Association of Child and Adolescent Psychiatry and Allied Professions (IACAPAP) world congress in Paris (Parry 2012e) and published a more refined version of the literature review (Parry 2012f; Appendix A19) on which Chapter 8 of this thesis is based.

Scepticism towards the PBD hypothesis within Australian and New Zealand child psychiatry appeared to be widespread, as it did in Europe, and this differed from the wide use of the diagnosis in the US. The scale of this concern has since been confirmed with the publication

of clinical diagnosis rates (Chapter 4.8.6.14). My impression about the apparent splitting along geographic lines in the field of child and adolescent psychiatry over this "notoriously controversial" diagnostic entity of PBD were illustrated in the number of presentations at different conferences. While there had been 40 presentations on PBD at the 2009 AACAP conference in Hawaii, there were zero at both the FCAP of the RANZCP annual meeting in Queenstown, New Zealand, and at the large European Society of Child and Adolescent Psychiatry (ESCAP) conference in Prague, Czech Republic in the same year: I attended the Queenstown conference, and my wife, Anja Kriegeskotten, and another Australian child psychiatrist, Lydia Rusch, both German speakers, while attending the Prague conference asked the two chief convenors, highly respected European child psychiatrists, why there were no presentations on PBD, to which the answer reportedly was "PBD is an American fad and it will pass". On a similar anecdotal note, I attended a social gathering of over 30 international attendees to the AACAP Hawaiian conference where the mood was one of incredulity on hearing of the diagnosing of PBD and medicating practices for very young prepubertal children that were being presented in many of the conference symposia.

Further anecdotal evidence indicated many US child psychiatrists never accepted the PBD hypothesis. For example, US colleagues I spoke to at AACAP 2009, and at other conferences since, stated it was difficult to get sceptical viewpoints published in journals like the *Journal of the American Academy of Child and Adolescent Psychiatry* (*JAACAP*) where PBD articles were numerous. The first sceptical symposium at an American Psychiatric Association (APA) conference, presented by three Californian child psychiatrists, Ed Levin, Mary Burke and Professor Glen Elliott, and me, took place at the 2009 APA conference in San Francisco. We titled it: "Pediatric bipolar disorder: A critical look at an American phenomenon" (Parry et al. 2009; Appendix A8). My personal recollection is of several hundred attendees in a large hall, and a vigorous debate followed with comments from the audience that reflected both pro-PBD and sceptical perspectives, with applause for comments in question time suggesting a roughly 50/50 split in perspectives.

When the APA annual meeting returned to San Francisco in 2013 a group comprised of Ed Levin, Stuart Bair and Professor Stuart Kaplan of Pennsylvania State University (author of *Your Child Does NOT Have Bipolar Disorder* (Kaplan 2011b) and myself presented another symposium: "Pediatric bipolar disorder in its historical context: An examination of reasons for

its controversial status." A smaller audience was in attendance, this time with the majority appearing sceptical of the PBD hypothesis, illustrative of what now appeared to be the passing of the peak for the PBD hypothesis in the US by that time (see Figure 4.1). During the same trip to the US we visited Boston and I met with child psychiatrists Professor Gordon Harper and Jennifer Harris (both affiliated with Harvard). Harris published one of the very early sceptical articles on PBD (Harris, J 2005). Both made clear that while the PBD hypothesis was dominant in their part of the US, there were departments and clinics that held to the 'conservative' perspective in Massachusetts.

The following year at the 2014 APA annual meeting in New York I attended a symposium presented by the PBD researchers from the Harvard affiliated Massachusetts General Hospital (MGH-Harvard) group led by Professor Joseph Biederman, arguably recognised as the leading academic proponent of PBD. Based on my literature review (Parry 2012f), I questioned Professor Biederman as to why his research group only briefly mentioned the word 'attachment' in text in a single article of 157 articles from his group on PBD. I reminded him that the passage was from a 1998 article where he and his co-authors stated that "a key limitation" of their study was they "did not assess for other disorders such as reactive attachment disorders that might present with manic symptoms" and that the article said they would investigate reactive attachment disorders in future (Biederman et al. 1998, p. 365). Professor Biederman replied that the "only reason" they had published "that paragraph" was that "a reviewer at the journal insisted on it".

I then asked Professor Biederman if he thought PBD researchers were missing maltreatment factors because they tended to find rates of child sexual and physical abuse in their clinical cohorts a full order of magnitude (around 1% for sexual abuse and 2% for physical abuse) below most community clinical prevalence studies (around 7 – 13% for sexual abuse and 10 – 25% for physical abuse) (May-Chahal & Cawson 2015; MacMillan et al. 1997; Pereda et al. 2009; Radford et al. 2013; Rosier 2017). This raises the issue of 'iatrogenic consequences' and questions of 'medical ethics', as child protection is a mandatory principle of good clinical and research practice, and failure to identify maltreatment may violate this. The editor of *The Lancet Psychiatry*, Niall Boyce, was in the audience; he commented as I was walking back to my seat that it was "a good question". This later led to an invitation to write an opinion piece

for *The Lancet Psychiatry*, an article which stands as something of a synopsis for this thesis (Parry, Allison & Bastiampillai 2015; Appendix A28).

While attending the 2014 APA conference in New York, I gave a grand round presentation on the internal drug industry documents to the child psychiatry department of New York University Langone Child Study Centre and a lecture on the history of psychiatric nosology to the psychiatric trainees there. Professor Jesse Shatkin of the department invited me to speak on their radio show, 'Child Psychiatry and Parenting Show: *About Our Kids'* where I aired the view that PBD was rarely used outside the US. Callers to the radio station, including some clinicians, expressed both pro-PBD and sceptical views. Both Shatkin and the head of the department, Professor Glenn Saxe, personally stated to me that several US child psychiatric academic departments had never entertained the PBD hypothesis; hence there was great variation within the US on whether the diagnosis was used clinically (J Shatkin, G. Saxe, 2014, conversation, 6 May). This was reiterated to me most recently at the 2018 AACAP conference in Seattle, where two of the local senior child psychiatrists, Professor Jon McClellan (University of Washington), whose vocal scepticism of the PBD hypothesis in both the US academic literature and media is reported in Part I of this thesis, and Associate Professor William French (University of Washington) conveyed to me that in French's words: "the child psychiatry department in this state deliberately kept the PBD theory out" from when it first arose in the 1990s (W. French, 2018, conversation, 26 October). Consequently, while the US child psychiatric literature has been dominated by pro-PBD articles and this could lead to the assumption that the hypothesis was widely accepted in the US, this may not necessarily be the case. The relative lack of sceptical literature makes it hard to gauge the extent of the 'conservative' perspective. French's comments suggest that local academic leadership played a role in acceptance or rejection of the PBD hypothesis.

Outside of the US, observations at international conferences suggested minimal adoption of the PBD hypothesis. Professor Harper, secretary of IACAPAP, invited me to co-present in a symposium on the history of psychiatric nosology and the importance of the biopsychosocial model at the IACAPAP World Congress in Beijing in 2010 (Harper 2010, Parry 2010b). At this conference Ellen Leibenluft, chief of the Section on Mood Dysregulation and Neuroscience at the US National Institute for Mental Health (NIMH) "showed that chronically irritable children who have been described by some researchers as 'broad phenotype paediatric bipolar

disorder' are better characterized as 'severe mood dysregulation' based on lack of conversion to classical bipolar disorder in follow-up studies" (Parry et al. 2010, p. 13; Appendix A14). Judging by applause, this presentation was positively received by a large audience. Given my interest, I closely read the conference programs and from recollection there were few presentations on PBD at the IACAPAP conferences I attended in Beijing (2010), in Paris (2012) or Durban (2014). At the 2012 Paris conference there was a debate concerning the validity of the PBD hypothesis, where Professor Benjamin Goldstein (University of Toronto/Pittsburgh University) presented in the affirmative and Professor David Coghill (University of Dundee) in the negative. Coghill noted he had never seen a prepubertal case of mania and interspersed his PowerPoint slides with stills from an episode of *The Simpsons* where Bart has been diagnosed with a new psychiatric disorder and put on new psychotropics that cause side-effects – until his mother Marge decides to take him off all the new drugs and just put him back on "good ol' Ritalin". The point was made, that attention-deficit hyperactivity disorder (ADHD) should not be misdiagnosed as PBD and treated with harsher medications, and the mostly European audience appeared greatly amused. I cite this personal observation as it highlights the vast gulf between the views on PBD expressed at these conferences and suggests that the classical conservative viewpoint continued to be held by the majority of non-US child psychiatrists.

At IACAPAP Paris 2012 there was a symposium conducted by Biederman and colleagues (Biederman & Wozniak 2012; Soutullo 2012; Joshi, Biederman, et al. 2012) at which I took notes. During question time I asked Professor Biederman if his group had looked at attachment patterns in their work on familial associations. He dismissed attachment theory, a bedrock theory of child development, as "philosophy, not science". His MGH-Harvard colleague, Gagan Joshi, in his presentation added that it was important not to return to the era of "parent-blaming" for children's behavioural problems and the third presenter on the panel, Professor Cesar Soutullo (University of Navarre, Spain) said there was "no time" for attachment-theory-related research. When a French psychiatrist asked Professor Biederman whether the group had looked for borderline personality disorder in the parents of the children with PBD or ADHD or control group, the reply was "no, next question?". To my mind these responses reflected the deficits that I had detected in the PBD literature, of not considering the contribution of children's environmental contexts to identified symptoms.

While at the 2012 IACAPAP conference, I had a brief conversation with Professor David Cohen (University Pierre et Marie Curie, Paris), convenor of the conference, who had an interest in the treatment of bipolar disorder and early psychosis (for example, as discussed in (Cohen et al., 2005)). Similar to the convenors of the ESCAP 2009 conference, he expressed the conservative view and believed there was minimal support for the PBD hypothesis in Europe (D. Cohen, 2012, conversation, 22 July).

Beyond Europe and the US

Conversely, there is the possibility that the PBD hypothesis is still gaining adherents in Latin America and Asia. Three posters were favourable to the liberal pro-PBD perspective from South Korea and Japan at the 2012 Paris IACAPAP conference. At the 2014 Durban IACAPAP conference there were only five PBD-related presentations. These included: a pro-PBD one by the president-elect of AACAP at the time, Professor Karen Wagner (University of Texas); a mostly pro-PBD key-note presentation titled "Paediatric bipolar disorder – what is the controversy?" by the sitting president of AACAP, Professor Paramjit Joshi (George Washington University); a pro-PBD presentation from China of neuro-imaging in bipolar depression by Professor Linyan Su (University of Beijing) that was later published (Gao et al. 2014); and a presentation of my own (Parry, 2014b) on preliminary bibliometric study of the geographic perspectives on PBD (Chapter 7) later published as Parry, Allison and Bastiampillai (2019b) (Appendix A35).

In 2011 I attended the Annual National Conference of the Indian Psychiatric Society (ANCIPS) in New Delhi. A symposium titled "Recent advances in the understanding of childhood bipolar disorder" was delivered by several child psychiatrists from Kolkata (Mondol et al. 2011). The presenters noted that PBD was "notoriously controversial" but presented much of the PBD literature with little critique. I found myself during question time politely talking at increasing length from the floor about alternative and sceptical views on the PBD phenomenon. The presenting panel were interested in what I had to say and afterwards we had a further discussion about sceptical perspectives for which they seemed genuinely grateful. Several members of the large audience came up to me afterwards and expressed gratitude for raising the sceptical perspective as they disagreed strongly with the pro-PBD views being expressed.

It is worth also noting here that Canadian child psychiatry, despite geographic proximity, remained mostly committed to the classical conservative perspective. In an email conversation with the editor of the *Journal of the Canadian Academy of Child and Adolescent Psychiatry (JCACAP),* Normand Carrey, I enquired as to how PBD was viewed amongst Canadian child and adolescent psychiatrists. He stated that a question often asked amongst colleagues is "where did you train?" as some who trained in certain settings would often be favourably disposed to the diagnosis. But he said that overall PBD did not catch on north of the US border. In a pithy email (N. Carrey, 2013, email, 9 February) he covered many of the factors that will be referred to in this thesis:

> "[T]o specifically answer your question why Bipolar has not caught on in Canada- these are my views- 1) as mentioned we follow more the British-Irish tradition, in Quebec its more France 2) we have more time to do assessments so by this virtue we have more time to cover psychosocial issues, 3) we are a small group (only 400 to 600 of us; so it's easier to get group coherency here), 4) by nature we are conservative – i.e. we are not inclined to polypharmacy 5) if anything it is more our pediatricians who are doing more polypharmacy, 6) we have socialized medicine!!?? i.e. a doctor or a specialist will get paid no matter what or how he prescribes 7) there are not as many researchers here whose salary depends on drug company money; more skepticism about Big Pharma 8) while admiring our US counterparts for some achievements, there is always a good dose of skepticism about causes embraced by Americans 9) many of us are familiar with both DSM and ICD."

He also commented on the US child psychiatrist practice of '15-minute med checks' (Williams 2008) not being an issue in Canada and stated he knew that in the US some psychiatrists were paid according to how many subjects they enrolled in research.

Highlighting the controversial nature of the PBD hypothesis and alluding to the iatrogenic consequences associated with it, another Canadian psychiatrist, Professor Joel Paris (McGill University, Montreal) and former Editor-in-Chief of the *Canadian Journal of Psychiatry* was reported to have stated in a presentation at the 165th annual meeting of the APA in Philadelphia the following:

> When psychiatrists 50 years from now look back on our current era in psychiatry, they will understand that the diagnosis of paediatric bipolar disorder is the greatest scandal to ever befall psychiatry. (Paris 2012)

This statement had been conveyed to me by Professor Stuart Kaplan (Pennsylvania State University), who was present at the APA meeting in his state. Professor Paris said "that is exactly what I said!" to my request for confirmation of this bold statement (J. Paris 2013, email, 27 September).

At time of writing this prologue, I had returned from the 2018 AACAP meeting in Seattle. What was lacking at the time of the emergence of the PBD hypothesis were the findings of long-term studies: this has now been rectified. From an ontological perspective the question of when and how mania, and thus the diagnosis of bipolar disorder, has its onset appears to now have been answered in a manner that supports the classical conservative perspective. A 2018 AACAP symposium covering the findings of several longitudinal prospective studies of high-risk offspring of adults with well characterised Bipolar-I disorder reveals the first manic episodes present from mid-adolescence onwards and are preceded by non-specific anxiety and sleep disorders (Duffy, Goodday, et al. 2018). The work in this area of Canadian researcher Professor Anne Duffy (Queen's University, Kingston) and other researchers in offspring studies is explored in detail in Chapter 4.8.7. The discussant for the symposium in Seattle was the current president-elect of AACAP, Professor Gabrielle Carlson (Stonybrook University, New York) who features prominently in the historical (Part I) section of this thesis and recently as co-editor of the nine-article debate on the PBD hypothesis in the journal *Child and Adolescent Mental Health* (Chapter 4.8.8.2).

This lengthy prologue regarding personal experience establishes how and why I have come to believe in the classical conservative perspective regarding what constitutes mania/bipolar disorder and the typical age of onset. I view the PBD phenomenon through this lens and this thesis is written from this perspective. Epistemologically I have approached the PBD phenomenon as a deviation from the normative body of knowledge that constitute the fields of child and adolescent psychiatry and developmental psychology and psychopathology. I present evidence that this deviation has led to iatrogenic consequences. These in turn raise

ethical questions and also have implications for psychiatric nosology as to how such a deviation from diagnostic practice could occur to the extent that it has.

Sociological perspectives

The thesis topic straddles psychiatry and sociology. Psychiatry as a discipline is no stranger to sociological critique. In particular I refer to a critique by a medical sociologist in *The Lancet* titled "A psychiatric revolution" (Scull 2012; Chapters 4.2.2; 9.4.1) who notes the extreme pendulum swings from biomedical to psychosocial paradigmatic perspectives within psychiatry both temporally and geographically. It is one reason why psychiatry as a field has strived to adhere to the 'biopsychosocial model' which its chief proponent, George Engel, argued would provide medicine and psychiatry with a conceptual approach that "should do much to mitigate the holist-reductionist dichotomy and improve communication" (Engel 1977, p. 134). Engel's article was titled "The need for a new medical model: a challenge for biomedicine". He linked the biopsychosocial model to general systems theory for a "fundamental reorientation in scientific perspectives in order to open the way to holistic approaches more amenable to scientific inquiry and conceptualisation" (p. 134). General systems theory emphasised holism over reductionism and organism over mechanism, and the importance of taking into consideration the interactions of all known variables, seeing biological organisms as 'open systems' that achieve 'steady states' in interactions with their environments (Von Bertalanffy 1950). In relation to psychiatry, symptoms might have psychosocial meaning in terms of origin and/or function. Engel was critical of "biomedical dogma" that "leaves no room within its framework for the social, psychological, and behavioural dimensions of illness" (p. 135).

The biopsychosocial model has been criticised for relying on eclecticism (Ghaemi 2009) and lacking an integrated pragmatic methodological approach (McLaren 1998), or not sufficiently including the cultural and spiritual/ontological domains and unable to stem the drift to biomedical reductionism (Pilgrim 2002). However, it has been defended for at least calling clinicians and researchers to consider all three domains of biological, psychological and social factors and laying a basis for a broad psychiatric training curriculum and providing a heuristic model for future refinement (Searight 2016; Benning 2015; Gask 2018).

The biopsychosocial model was the template for much of my own training in the RANZCP curriculum. It is my impression that the PBD hypothesis grew in a biomedical reductionist environment that under-emphasised the psychological and social domains. Searight (2016) attributes the persistence of biomedical reductionism to the time pressures of the health system, at least in the US, that led some medical school clinical curriculums to be dismissive of it. Searight (2016) notes:

> By the mid 1990s, with growing demands for efficiency, genuinely knowing one's patients became a luxury that a physician could ill afford (Biderman et al. 2005). (p. 294)

This period corresponds to that of the PBD phenomenon, and from a sociological perspective medicine and psychiatry were under pressure to 'get on with it' and not focus on the psychosocial environment of patients.

In terms of the social domain, a sociological epistemology and methodology could have been used to structure this thesis. The work of Niklas Luhmann (Luhmann 1986) and Pierre Bourdieu (Bourdieu 1977) describe how movements and organisations arise through the process of 'autopoiesis' (self-creation) whereby self-referential theories and communication practices perpetuate the organisation and its beliefs. As Bourdieu describes, forms of knowledge have hegemonic value (Bourdieu & Passeron 1990) and Luhmann describes how adherents to a particular theory gather to create hermetically sealed self-referential systems where the ideas communicated are "recursively produced and reproduced by a network of communications, and which cannot exist outside of such a network" (Luhmann 1986, p. 174). The bibliometric reviews in Part II illustrate this. The geographical spread of the PBD hypothesis (Parry, Allison & Bastiampillai 2019b; Appendix A35; Chapter 7) has been limited and mostly involved direct collaboration by PBD researchers across national boundaries. The apparent choice by the PBD research community to ignore the traditional and established topics of psychosocial developmental trauma and family systems theory research (Chapter 8) illustrates an adherence to the biomedical model rather than the more systemic biopsychosocial model. The self-referential aspect is reflected in that the PBD literature only cites three psycho-educative family approaches developed by PBD researchers for children already diagnosed with PBD and neglects the thousands of articles on family systems and parent training research.

In sociology and criminology, the work of Sykes and Matza (1957) postulated how groups justify behaviour that breaches moral or common-sense norms by 'techniques of neutralization'. If the time and diagnostic upcoding pressures of health systems and dependency on research grants from the pharmaceutical industry lead to a concentration on children's behaviour as biologically determined pathology and an avoidance of consideration of psychosocial stressors in children's lives, then clinicians and researchers might justify themselves, and 'neutralize' this oversight, as doing the best for the children in the circumstances. Ashforth and Anand (2003) examine the group dynamics whereby corruption and malpractice become normalised in large organisations through the use of "rationalising ideologies" (p. 16). These could explain the conflicts of interest problem that was identified by the US Senate Finance Committee investigation as being particularly associated to some PBD-research academic departments (see Chapters 4.7; 4.19; 4.21). Although PBD researchers undoubtedly want to provide best care for children and youth, and see themselves as discovering a previously neglected high rate of childhood bipolar disorder in need of treatment, a group-think via an echo-chamber of published literature and continuing medical education can reinforce a biomedical reductionist viewpoint to the degree that the psychosocial domains seem to have been not just neglected but forgotten (see Chapter 8).

Cultural perspectives

A further alternative approach that could have guided the structuring of this thesis would have been to explore PBD as a 'culture-bound syndrome'. In psychiatry 'culture-bound syndromes' are used to describe psychiatric disorders that occur due to cultural factors, generally in exotic indigenous communities and developing countries (Levine & Gaw 1995). Examples include the following disorders: "Koro", a group hypochondriasis that occurs in epidemics in parts of south-east Asia where men start to believe that their penises are shrinking into their abdomens; "Dhat", occurring in India and associated with anxiety and fatigue in men related to fear of losing too much semen; "Bebainan", where young women from Balinese nobility, who culturally are expected to behave with extreme politeness, vent their anger in seemingly irrational brief rage attacks. The last of these can be seen to have a useful function for individuals whose emotional lives are otherwise highly socially constrained.

The DSM-IV defined culture-bound syndromes thus:

> The term *culture-bound syndrome* denotes recurrent, locality-specific patterns of aberrant behaviour and troubling experience that may or may not be linked to a particular DSM-IV diagnostic category. Many of these patterns are indigenously considered to be "illnesses," or at least afflictions, and most have local names. Although presentations conforming to the major DSM-IV categories can be found throughout the world, the particular symptoms, course, and social response are very often influenced by local cultural factors. In contrast, culture-bound syndromes are generally limited to specific societies or culture areas and are localized, folk, diagnostic categories that frame coherent meanings for certain repetitive, patterned, and troubling sets of experiences and observations (DSM-IV, APA, 1994, p. 844).

While the previous examples provided refer to less-developed societies, culture-bound syndromes can also be found in advanced societies: modern Japan has, through the impact of computers and the internet, seen an increase in a newly named disorder, *Hikikomori*. This disorder refers to adolescents, almost exclusively males, who hide away in their rooms and may become lifelong recluses. The dynamics involved in the disorder are hypothesised to be several: traditional Japanese familial dependency, in particular close mother-son relationships; the intense pressures of the Japanese educational system and later the corporate business world, both in terms of performance and pressure to conform socially with an entrenched culture of bullying; the Japanese economic stagnation and unemployment problem of the past two decades; and persisting middle-class affluence that allows for the young man to stay at home (Furlong 2008).

Within this field of 'cultural psychiatry' there has been a broadening of perspective since the 1970s with a landmark article that compared the somatisation syndromes in China with the depressive syndromes in the US, to reveal the cross-culturally relative nature of illness behaviour (Kleinman 1977). The Western-centric view of culture-bound syndromes described in the DSM has been critiqued as a form of colonialism, with a blindness to the "disease essentialism" and "universalism" inherent in the Western medical paradigm (Kirmayer 2007, pp. 7-8), and Western culture and Western biomedicine is itself a form of ethno-psychiatry that can be studied for its own syndromes and diagnosing practices (Timimi & Maitra 2009).

Timimi and Maitra critique an example of a form of Western ethno-psychiatric imperialism or colonialism, outlined in the "Global consensus on ADHD/HKD" (hyperkinetic disorder), which was co-authored by a 'Global Working Group' of 15 prominent ADHD researchers (Global ADHD Working Group 2005).

For PBD to be identified as a culture-bound syndrome of the US, there are likely to be a number of contributing factors, similar to Hikikomori in Japan. However, strictly speaking, for this to happen, PBD would need to be seen only in the US. Hikikomori resembles a pattern of school refusal and agoraphobia commonly seen in other developed nations, but the extreme nature of the disorder in Japan reflects culturally specific precipitating and perpetuating factors. The symptoms of the proposed PBD diagnosis, such as chronic irritability, disruptive behaviour, ADHD symptoms, affect dysregulation including 'silly, giddy and goofy' anxious excitement and appeasing defences, are clearly not idiosyncratic to children and adolescents in the US. However, many child psychiatrists and other mental health specialists both in the US and around the world would not diagnose these children and young people with PBD, but would explore the contextual origins of their symptoms and likely diagnose other disorders, for example: parent-child relationship problem, oppositional defiant disorder (ODD), ADHD, anxiety disorders, major depressive disorder (MDD), dysthymia, responses to trauma and maltreatment including post-traumatic stress disorder (PTSD), and reactive-attachment disorder.

One of my supervisors, Professor Jon Jureidini, suggested it may be more appropriate to coin a new term for the PBD phenomenon, that of a 'culture-bound diagnosis'. In other words, the issue is not one of a consistent syndrome with unique symptoms, but rather appears to be the localised ethno-psychiatric diagnosing practices emanating from certain US child psychiatry departments and the US health system and public media context they occurred in.

A methodology derived from a systemic clinical approach

What struck me about the PBD hypothesis and the research and clinical milieu within which it found fertile ground, was the lack of the systemic biopsychosocial approach. This holistic biopsychosocial diagnostic formulation approach has historically been the foundation of psychiatric diagnosis across the globe: it considers presenting symptomatology accompanied by predisposing, precipitating, perpetuating and protective contextual factors. It does not

replace, but rather, complements and provides deeper explanatory context to the descriptive diagnostic approach of the DSM and the ICD. This aspect is expanded upon in Chapter 9.4. A hallmark of the PBD research literature is the primacy given to the sole use of descriptive symptom-based diagnostic practice while neglecting the contextual information essential for an accurate diagnosis.

The aim of this thesis is to provide an understanding of what the PBD phenomenon was, how it came to be, and what lessons can be learnt so that psychiatry does not repeat the mistakes that led to an epidemic of misdiagnosing and overmedicating many thousands of young children with a rare serious mental disorder that almost invariably has its onset after mid-adolescence. As a clinician, I have chosen in this thesis to use the same case formulation methodology to assess the PBD phenomenon as has been my training and practice as a psychiatrist: in short, take a comprehensive chronological history of the symptoms (the way the PBD hypothesis arose and spread in clinical practice) in their environmental context (Part I); examine features of the PBD phenomenon, by way of metaphor, the 'patient's mental state', via a re-analysis of a key meta-analysis and bibliometric analyses of the PBD literature) in some depth (Part II); then bring all the relevant factors together in a coherent diagnostic formulation (how and why the PBD phenomenon occurred and what it means) that considers context and interaction of factors (Part III). To use such an approach in a thesis may have been somewhat unconventional, but the alternatives of a sociological or cultural analysis would have been beyond my expertise.

In applying this methodology, the thesis has been structured as follows. Part I provides the necessary background context, commencing with the chronological history of the classical view of bipolar disorder (Chapter 1 & 2), and then demonstrates how the PBD hypothesis deviated from this: how it arose, the extent to which it grew in influence, and the contextual factors that were contributed to its growth (Chapter 3 & 4). While not a complete history, these two chapters nonetheless are the most comprehensive account of the events over the past quarter century that comprise the PBD phenomenon. Such a chronicle is an aim in itself of this thesis. The events that comprise the PBD phenomenon and epidemic are analysed in Chapter 5 along with the rationale for exploring three aspects of the phenomenon with new research. Part II examines these three aspects of the PBD literature in depth that add insight into some of these contextual factors. The methodology for these literature reviews is

outlined for each aspect: the epidemiology of bipolar disorder in the paediatric age range (Chapter 6); the geographical pattern of spread of the PBD hypothesis (Chapter 7); the degree of reference to attachment, trauma and maltreatment factors in the PBD literature (Chapter 8). In Part III, the conclusions drawn and their implications for the legitimacy of the PBD phenomenon are discussed. Concerns are raised regarding the subsequent iatrogenic consequences and medical-ethical implications, and an exploration of why psychiatric nosology was not robust enough to contain the PBD hypothesis before its premature translation into a clinical practice epidemic. In the Conclusion these strands are brought together in a "Dynamic diagnostic formulation of the PBD phenomenon". As in a comprehensive systemic diagnostic formulation, the aetiology of the problem is made manifest and a management plan flows naturally from this.

It is also important to note that the PBD researchers had a noble goal. It was to intervene early to nip what was interpreted as an emerging serious mental illness in the bud. From clinical experience, I recall treating close to twenty adolescents suffering Bipolar-I and Bipolar-II disorders with classical mania and hypomania episodes. It is an uncommon but potentially devastating illness. Often the disorders started with a prodrome of mood lability, particularly depressive symptoms. However, mood lability is a ubiquitous problem in adolescence and not uncommon in prepubertal children. It is vital that the antecedents are identified to enable early detection and intervention for bipolar disorder. While the most recent research (Duffy et al. 2017; Chapter 4.8.7) suggests that these have been identified as anxiety and sleep disorders, unfortunately these are non-specific to later bipolar disorder, though in children of parents with bipolar disorder it suggests increased vigilance is warranted. Meanwhile, it is equally vital not to diagnose, label and medicate those for whom it is incorrect to do so. I have seen children and adolescents who were erroneously diagnosed with deleterious consequences as well. Hence the PBD debate is both crucial and complex, and this is reflected in this thesis that seeks to cover the gamut of the issues surrounding this "notoriously controversial" diagnosis.

Contents

List of Figures

Note that where copyright is not obtained, figures shall appear blank with note 'copyright not obtained' in the publicly published version of this thesis.

List of Abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
ADHD	Attention-Deficit Hyperactivity Disorder
ANZJP	*Australian and New Zealand Journal of Psychiatry*
APA	American Psychiatric Association
ASD	Autism Spectrum Disorder
BRIDGE	Bipolar Disorders: Improving Diagnosis, Guidance and Education study
CABF	*Child and Adolescent Bipolar Foundation*
CAMH	*Child and Adolescent Mental Health* (journal)
CAPA	Child and Adolescent Psychiatric Assessment (questionnaire)
CBCL	Child Behaviour Checklist (questionnaire)
CBQ	Child Behaviour Questionnaire (questionnaire)
CD	Conduct Disorder
CDC	CENTERS FOR DISEASE CONTROL AND PREVENTION
CGAS	Child Global Assessment Scale (questionnaire)
CIDI	WHO Composite International Diagnostic Interview (questionnaire)
CME	Continuing Medical Education
CMS	(CMS), CENTERS FOR MEDICARE & MEDICAID SERVICES
DAWBA	Development and Well-Being Assessment (questionnaire)
DICA	Diagnostic Interview for Children and Adolescents (questionnaire)
DISC-IV	Diagnostic Interview Schedule for Children, version IV (questionnaire)
DMDD	Disruptive Mood Dysregulation Disorder
DSM	"Diagnostic and Statistical Manual of Mental Disorders" of the APA (editions: I, II, III, III-R, IV, IV-TR, 5; first, second, third, third-revised, fourth, fourth-text-revision, fifth)
FAERS	Food and Drug Administration Adverse Event Reporting System
FDA	Food and Drug Administration
FCAP of RANZCP	Faculty of Child and Adolescent Psychiatry of the Royal Australian and New Zealand College of Psychiatrists
IACAPAP	International Association of Child and Adolescent Psychiatry and Allied Professions
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases - Version 10
ISBD	International Society for Bipolar Disorders
JAACAP	*Journal of the American Academy of Child and Adolescent Psychiatry*
JBRF	Juvenile Bipolar Research Foundation
KOL	Key Opinion Leader
K-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia (questionnaire)
MGH-H	Massachusetts General Hospital, a division of Harvard University
NIMH	National Institute for Mental Health
ODD	Oppositional Defiant Disorder
OECD	Organisation for Economic Co-operation and Development
PBD	Paediatric Bipolar Disorder
RANZCP	Royal Australian and New Zealand College of Psychiatrists

SDQ	Strengths and Difficulties Questionnaire (questionnaire)
SMD	Severe Mood Dysregulation
WHO	World Health Organisation
WUSL	Washington University in St Louis
YMRS	Young Mania Rating Scale (questionnaire)

List of Appendices

Appendix A: Publications relevant to this thesis.

Appendix B: Timeline of key PBD articles and events.

Appendix C: Citation tree articles used in Chapter 7 plus further data analyses.

Appendix D: Selected pharmaceutical industry documents and correspondence.

PART I OVERVIEW OF THE 'PAEDIATRIC BIPOLAR DISORDER' PHENOMENON

Following the introduction where the scope of this thesis is outlined, the chapters in this section first provide a historical background on views within psychiatry of the diagnostic boundaries of mania and bipolar disorder generally and in children and adolescents specifically. The rise of the PBD hypothesis of atypical mania in young children is then described. Debates over the definition and boundaries of bipolar disorder in the paediatric age range, provoked by the PBD hypothesis, are presented in a thematic and chronological framework with a focus on significant published articles and notable debates in the academic literature. As the rate of diagnosis of PBD escalated and attracted controversy, debates at conferences and in the media are also relevant background to understanding the PBD phenomenon and are therefore presented as well.

INTRODUCTION

> *The rate of psychotropic agents being prescribed to pre-schoolers is skyrocketing… Labelling severe tantrums in toddlers as a major mental illness lacks face validity and undermines credibility in our profession.*
>
> Dr Jon McClellan
> Commentary to the "Treatment Guidelines for Child and Adolescent Bipolar Disorder"
> *Journal of the American Academy of Child and Adolescent Psychiatry*, March 2005; 44:236-239

Aims of this thesis

The PBD overdiagnosis epidemic is so extraordinary that to understand it and explore the implications of how it came to be and how to prevent future such overdiagnosis epidemics is a large topic. Therefore the aims of this thesis are broad: 1) to provide the fullest chronicle of the PBD epidemic to date; 2) to explore the three research questions outlined below for their capacity to shed further light on the PBD epidemic; 3) to synthesise and understand the PBD epidemic and its implications for medical ethics (particularly conflicts of interest) and psychiatric nosology (how it was unable to prevent misdiagnosis on such a scale), as failures in these two domains were the likely reason for the epidemic's manifestation.

The critical consequences of the proposed PBD diagnosis

Early detection of mental disorders is a vital goal that potentially allows for early intervention and treatment that, in turn, can improve quality of life and decrease early morbidity. Alternatively, over-diagnosis and misdiagnosis of mental disorders can engender damaging iatrogenic consequences: through detrimental physical effects via inappropriate pharmacotherapy; though detrimental psychological effects of labelling; and through other causes of mental and behavioural problems being overlooked and not addressed.

Bipolar Disorder is a serious mental disorder that has had longstanding recognition in the internationally recognised health classification systems of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, currently in its 5th edition (DSM-5; APA 2013b), and the World Health Organisation's (WHO) International Classification

of Diseases, currently in its 10th edition (ICD-10; WHO 1992). Definitions differ slightly between editions of DSM and ICD, however in both documents the diagnosis requires episodes of mania or less severe hypomania. Depressive episodes are usually part of the illness, as are sometimes mixed depressive/manic episodes, however mania and hypomania define the disorder. Mania involves a severe episode of mental illness characterised by dramatic increases in energy, euphoria and elation sustained for at least a week and causing marked impairment in functioning, while hypomania is the same but to a lesser degree and sustained over at least four days (DSM-5) or for a few days (ICD-10). German psychiatrist Emil Kraepelin was a pioneer in defining the disorder, naming it "Manic-Depressive Insanity" (Kraepelin 1921).

It has been a consensus view in world psychiatry that mania or hypomania rarely if ever present prior to puberty and most commonly have onset in late adolescence through to young adulthood (Angst & Sellaro 2000, p. 446). Kraepelin's landmark study of 903 sufferers of Manic-Depressive Insanity found that 0.4% reported onset by age 10 years and a further 2.5% by age 15 years, with over 50% by age 30 years. It has been clinical practice since the 1950s that episodes can be ameliorated or prevented by the maintenance administration of lithium, or more recently by anticonvulsant 'mood stabilisers': hence early correct diagnosis and treatment is important.

In the mid-1990s, two separate groups of researchers in the US reported they had detected significant numbers of cases of pre-pubertal mania, including in very young children, at prevalence rates much higher than previously found. The large cohort studies undertaken by these two academic departments were published in US child psychiatry literature: their findings were a substantial departure from the established view that onset was primarily in late adolescence to young adulthood.

The researchers described phenomenology that differed substantially from adult bipolar disorder phenomenology. Two phenomenological 'phenotypes' were hypothesised: one of ultradian cycling of mood (multiple episodes per day) (Geller, Fox & Clark 1994), and the other of chronic non-episodic irritability (Wozniak, Biederman, Kiely, et al. 1995). For both these phenotypes the terms "juvenile bipolar disorder" (JBD) (Biederman 1995), and "paediatric bipolar disorder" (PBD) (Chang & Ketter 2001) were coined. Over time PBD came to be the

more widely used. Ultradian-cycling of euphoric and depressed mood states came to be described as “narrow phenotype PBD” and the chronically irritable condition as “broad phenotype PBD” (Pavuluri, Birmaher & Naylor 2005).

If these postulated phenotypes were true identifications of early cases of bipolar disorder, this could have been a major advance for the field. Such an early understanding of why the child has symptoms, and early administration of a medication like lithium or sodium valproate (an anticonvulsant mood stabiliser), could improve quality of life for those affected and their families, and reduce morbidity. However, if a serious mental illness, such as bipolar disorder, were misdiagnosed and over-diagnosed in the paediatric age range, then the potential for serious adverse consequences would be unacceptably high. Young children in the early stages of physical, cognitive, and psychosocial development, so misdiagnosed, may be irrevocably affected by the effects of psychotropic medications on all aspects of their still-developing selves, including their minds and bodies and cognitive abilities. They may also suffer a diminished sense of self-agency and altered development of sense of self, as well as the effects from altered parental and other carer expectations and the possibility of stigma. Further, such misdiagnosis may lead to other and correct diagnoses being overlooked, such as learning disorders or attachment and trauma and maltreatment problems, thus impairing early detection and specific intervention for these factors and leading to negative outcomes.

Reification of the PBD hypothesis and rapid translation into US clinical practice

The PBD hypotheses differed radically from the current accepted clinical wisdom as summarised in the 4th edition of the DSM (DSM-IV; APA 1994) or ICD-10. The PBD hypotheses were at times described in the literature under the Bipolar – Not Otherwise Specified (Bipolar-NOS) category because they did not meet criteria for Bipolar-I or Bipolar-II disorders. The Bipolar-NOS category also points to the concepts of ‘bipolar spectrum disorders’ and ‘soft bipolarity.’ These concepts continue to be highly controversial within adult psychiatry (Chapter 1.2). However, the proponents of PBD often described the PBD constructs in the academic literature as Bipolar-I (Geller et al. 2008), and PBD was frequently described as full mania (Biederman 1998a).

Adding a further degree of confusion, the 'narrow' and 'broad' phenotypes of PBD were sometimes combined by authors. It was not always clear to what extent pre-pubertal children were being included under the term 'PBD', but overall a key aspect of the PBD literature is an assumption that pre-pubertal children are often affected. This thesis will therefore refer to the term 'PBD hypothesis' as an overarching term, and where relevant refer to one or other of the postulated phenotypes.

While the DSM is a product of the American Psychiatric Association (APA), it is utilised internationally. In the US, the formal adoption of any new diagnostic hypothesis would normally require a significant degree of replicated and independent research confirmation, extensive discussion in the literature, and review by a DSM committee, and, if validated, incorporation into the DSM before translation into clinical practice. Reification is the process where giving a concept, construct or process a name generally results in the assumption it has ontological existence as a genuine entity. The introduction to DSM-IV offers cautions about absolute reification of psychiatric diagnoses: "there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries" (p. xii). Nonetheless a degree of reification of psychiatric diagnoses seems inevitable, particularly when formally ratified in the DSM or ICD manuals.

However, formal ratification did not emerge with the proposed PBD diagnosis. Instead, the PBD hypothesis received strong support through multiple publications in the *Journal of the American Academy of Child and Adolescent Psychiatry* (*JAACAP*) and other journals. Statistics of diagnosing rates indicate it soon came to be reified as a disease entity in the minds of many US clinicians and adopted into widespread clinical practice (Blader & Carlson 2007; Moreno et al. 2007).

The concept was also given some credence by the US National Institute for Mental Health (NIMH) (Notelmann et al. 2001). Further credibility was created with the provision of online CME (continuing medical education) tutorials for practitioners, and PBD presentations featured highly at US psychiatric conferences (Healy & Le Noury 2007; Chapter 4.2.2). PBD was reified in the mind of the US public through promotion by an advocacy organisation, the *Child and Adolescent Bipolar Foundation* (CABF) (Resko 2011b), self-help books for parents and story books for supposed child sufferers (Chapter 4.3.4). In 2000 PBD featured on the

Oprah Winfrey Show (Chapter 4.4.1). PBD, also known to the US public as 'childhood bipolar', became widely known and associated with a belief that it indicated a chemical imbalance in children's brains, as was even advertised during children's cartoon TV (Chapter 4.4.3): many parents wanted to know if their child's behavioural problems were in fact bipolar disorder.

Within the US health system, reimbursement for health care provision mostly depends on the diagnosis (Case et al. 2007). A PBD diagnosis, with the presumption of a serious mental illness like well-established Bipolar-I disorder, allowed greater access to US health services than a diagnosis, for instance, of Conduct Disorder (CD) (Blader & Carlson 2007). Behavioural problems, often associated with family dynamic conflicts, have been poorly reimbursed if at all in the US managed care health system (Harrison, Cluxton-Keller & Gross 2012). To date, despite the lack of formal reification by adoption into DSM-5, it may be that more than a million children and teens in the US have been diagnosed with PBD over the past two decades (McDonnell & Wozniak 2008; Chapter 4.3.5).

Evolution and devolution of 'broad phenotype' and 'narrow phenotype' PBD

In the past two decades, a large body of academic literature has accumulated on PBD. The vast majority of articles continue to be favourable to the 'narrow phenotype' PBD hypothesis. The PBD literature has also continued to sustain the assertion that pre-pubertal children, including very young children, periodically develop hypomania and mania (Goldstein et al. 2017).

The 'broad phenotype' PBD hypothesis of chronic irritability was widely applied for over a decade. It was then renamed by some researchers as "severe mood dysregulation" (SMD) (Brotman et al. 2006). The SMD construct was eventually modified and formally incorporated into DSM-5 as Disruptive Mood Dysregulation Disorder (DMDD) (Chapter 4.8.5). Despite this, articles referring to 'broad phenotype' PBD as constituting Bipolar-I disorder have still been published in journals such as *Bipolar Disorders* (Wozniak et al. 2017) and the *Journal of Affective Disorders* (Biederman et al. 2014).

Most recently, a review article in the journal *Bipolar Disorders* was authored by 18 proponents of PBD, who formed a task force on PBD for the International Society for Bipolar Disorders

(ISBD). Their report seeks, according to its title, to provide an insight into PBD, in particular, "[of] knowledge to date and directions for future research" (Goldstein et al. 2017). The task force authors appear to have subsumed the 'narrow phenotype' PBD hypothesis into the wider 'bipolar spectrum disorders' concept. They suggest that "ultradian cycling" is more likely to "describe mood fluctuations within an episode" (p. 527), rather than there being distinct episodes as had been originally hypothesised and often described. With regards to what was previously 'broad phenotype' PBD, the report argued that even if a DMDD diagnosis is made, that bipolar disorder should still be considered. This is despite DSM-5 stipulating DMDD to be an exclusion criterion for bipolar disorder. The authors assert that there has been "tremendous growth in the scientific literature regarding… PBD" (p. 524), and that the PBD diagnosis is well established, community epidemiological studies reveal high rates, that atypical antipsychotic drugs are first line therapy, and their report seeks to "dispel" the "myth" that PBD is still a controversial diagnosis (p. 525) (Chapter 4.8.9.3).

Idea formation and motivation for this thesis

As described in the Prologue, I have closely followed the debate on PBD since 2006. Over this time period, three critical observations evolved:

1. The PBD hypothesis remains highly controversial with many clinicians questioning its validity, particularly in pre-pubertal children; widely varying results are published regarding epidemiological and clinical prevalence rates.
2. There is a distinct international difference between much of the academic opinion and clinical practice in the US compared with most other nations; and
3. The contextual factors of possible attachment, maltreatment and developmental trauma have been mostly overlooked in the PBD literature.

Additionally, in researching the rise of the PBD phenomenon, it became obvious significant controversy existed about the role of the pharmaceutical industry in promoting PBD and potential conflict of interest for some PBD researchers: this was the subject of a US senate committee inquiry in 2008 (Grassley 2008) and subsequent media reports (Chapters 4.2; 4.6; 4.7). These events coincided with high profile litigation involving several large pharmaceutical companies from which internal company documents were released: a study of these pharmaceutical industry documents conducted by a US colleague and myself revealed,

amongst other issues, how some companies strategized to increase the number of bipolar diagnoses made in order to lift sales of their on-patent atypical antipsychotics (Spielmans & Parry 2010; Appendix A10).

Three research questions examined in this thesis

In this thesis, the three observations listed above are tested and presented. Each has a chapter devoted to the hypothesis in question. Each chapter corresponds with a published article: Chapter 6 (Parry, Allison & Bastiampillai 2018a; Appendix A31); Chapter 7 (Parry, Allison & Bastiampillai 2019b; Appendix A35); Chapter 8 (Parry 2012f; Appendix A19).

Are the findings of a highly cited meta-analysis of epidemiological studies of bipolar disorders in youth valid?

This question (Chapter 6) examines whether a widely cited meta-analysis of 12 epidemiological studies, which found a "1.8%" community prevalence for 7 – 21-year-olds for "PBD", (Van Meter, Moreira & Youngstrom 2011, p. 1250) is valid. A re-analysis of the original epidemiological surveys was undertaken by me, and a journal article was co-authored (Parry, Allison & Bastiampillai 2018a; Appendix A31). It was apparent that varying methodologies and assessment protocols had been used, making the combination of studies arguably unsuitable for statistical meta-analysis. Specifically, three areas of concern were identified: firstly, differences between studies in the utilisation of informant concordance and impairment criteria; secondly, disparity between studies regarding age of participants, with particular reference to pre-pubertal children; and thirdly, follow-up community studies of young people with a diagnosis of hypomania or Bipolar-NOS that assessed whether or not the disorder continued into adulthood were not consistently undertaken.

More recently, the ISBD Task Force (Goldstein et al., 2017) delivered a report that added six extra epidemiological surveys to the original study, leading to a claim of an increased community prevalence rate of 2.06% for PBD, although the same methodological issues were apparent (Parry, Allison & Bastiampillai 2018b; Appendices A33 & A36). The ISBD Task Force prevalence estimate was further increased to 3.9% by a meta-analysis that included another two epidemiological studies in addition to the six extra surveys as well as removing one of the

original 12 surveys (Van Meter et al., 2019b). Once again similar methodological issues could be critiqued (Parry et al., 2019c; Appendix A36; Chapter 6.8).

While the results are discussed in detail in Chapter 6, it is useful to note here the reworking of the main research data in this study, repeatedly referred to in support of PBD by its proponents, demonstrated a different conclusion, that being: consistent with the historically well-established view, mania and hypomania have a late adolescent or adult onset and are relatively rare conditions. This matter was the subject of a nine-article debate section in the journal *Child and Adolescent Mental Health* which is discussed in Chapter 4.8.8.2.

How widely has the PBD hypothesis been accepted in the international literature?

The PBD literature appears to have been dominated by authors from some US institutions. Further, there is a large discrepancy in the number of PBD papers presented at US child psychiatric conferences compared with non-US conferences (Chapter 9.5). International diagnostic rates of bipolar disorders in the paediatric age range show marked differences between the US and other countries (Chapter 4.8.6.14). Surveys of child psychiatrists in Germany and Australia and New Zealand showed majority scepticism of the PBD hypothesis (Meyer et al., 2004, Parry et al., 2009). A transatlantic comparison of diagnosis of clinical vignettes by US compared with UK child psychiatrists revealed a similar deviation in practice: support for the PBD hypothesis was mixed amongst US clinicians while minimal amongst UK clinicians (Dubicka et al., 2008; Chapter 4.8.6.6).

It is concerning if there is poor international agreement on the diagnosis and treatment of bipolar disorder in childhood and adolescence. Any major international differences in case conceptualisation may have a major impact on the clinical care of children and adolescents presenting with mood lability. If so, child mental health treatment will depend largely on nationality. In the US for example, the prescription rates of atypical antipsychotics rose in association with the marked increase in the rates of PBD diagnosis (Dusetzina et al., 2012; Lohr et al., 2015).

To formally test the hypothesis that there is a divergence of opinion between US and non-US child psychiatry on the subject of the PBD hypothesis, a bibliometric analysis of a body of PBD

literature was undertaken (Chapter 7) and recently published (Parry et al., 2019b; Appendix A35). A citation tree of 835 articles, that had cited one or more of four seminal early PBD articles, was compiled using the database *Web of Science* of which 787 were assessed as related to the topic. The 787 articles were then sorted according to authors, source titles (e.g. the publishing journal), affiliated institutions of the authors, authors' nationalities and publication year. Additionally, given the contentious debate about the validity of the PBD hypothesis, the articles' abstracts or full text were read to ascertain the perspective of the authors. The articles were assigned a designation as to whether they were either:

- in favour of the PBD hypothesis
- overtly sceptical of the PBD hypothesis
- using the previously well-established traditional perspective of bipolar disorder arising in mid to late adolescence, without being overtly sceptical
- about SMD/DMDD rather than PBD per se
- attempting to achieve a consensus view, or
- not applicable to PBD and had incidentally cited one of the four seminal papers for another reason.

This methodology allows for a bibliometric analysis that could compare the perspectives of articles. The perspective of opinion on PBD was compared according to authors, institutions, countries and publishing journals. In particular, the geographic spread of the PBD hypothesis and how it had been received was investigated.

Does the PBD research literature fail to consider context, specifically: attachment theory, developmental trauma and maltreatment factors?

One of the few early sceptical articles on PBD, from which the quote at the start of this chapter is taken, argued that proponents of the PBD hypothesis had not taken into consideration the developmental and family systemic context of children's moods and behaviour. McClellan reminded readers that children's emotional and behavioural problems are "complex" and "interwoven with temperament, attachment, parent-child relationships, cognition and other moderating and mediating factors including trauma" (McClellan, 2005). Such fundamental aspects of child psychiatry, developmental child psychology and psychopathology appeared

to be rare in the PBD literature. If the PBD research literature had not sufficiently considered attachment insecurity, maltreatment and developmental trauma as possible aetiological factors for emotional and behavioural dysregulation, then such dysregulation could have been incorrectly diagnosed as PBD.

To test this hypothesis, a bibliometric literature review of PBD related articles was conducted (Parry, 2012f; Appendix A19; Chapter 8). The articles were searched within the domains of "Title-Abstract-Keywords-References" for presence of the terms: *attachment, PTSD, trauma, maltreatment, child abuse, sexual abuse, physical abuse, emotional abuse,* and *neglect*. A similar search was also conducted on a body of SMD/DMDD related articles, and for comparison a body of attachment theory literature was searched for the presence of PBD terms.

The significance of these research questions

Iatrogenic consequences of a PBD 'epidemic'

These three research questions relate to critical areas of child psychiatry (epidemiology, differential diagnosis and case conceptualisation). Answers to these questions may have wider implications for the assessment and treatment of children and adolescents who present to mental health services with mood lability, and for the discipline of child psychiatry itself. The chair of the DSM-IV Task Force, Professor Emeritus Allen Frances strongly critiqued PBD in an opinion article titled: "Psychiatric diagnosis gone wild: The 'epidemic' of childhood bipolar disorder" (Frances, 2010b). Frances used the term 'epidemic' to describe over-diagnosis of psychiatric disorders particularly in child psychiatry. He highlighted the iatrogenic consequences of both medications and labelling on child development, as well as the failure to address other causes of irritability. He described "two other false epidemics" of Attention-Deficit Hyperactivity Disorder (ADHD) and autistic spectrum disorders (ASD) (p. 1.) but was concerned with PBD because of use of "harmful" medications that induce metabolic changes, as well as the long-term stigma of an erroneous bipolar disorder diagnosis (p. 2).

One of the most tragic examples of such iatrogenic consequences occurred in late 2006, when a 4-year-old girl diagnosed with PBD died due to an incorrect dosage of psychotropic medication. Following this, the iatrogenic consequences of the proposed PBD diagnosis

became a matter of debate by clinicians and academics in the public media, occurring mainly in the *Boston Globe* and *New York Times* (Chapter 4.6). Subsequent research into the psychotropic medicating of US children indicated problems with iatrogenic morbidity, particularly from atypical antipsychotics (Zito et al., 2008, Strayhorn, 2006, Ray et al., 2018). An analysis of the US Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) revealed atypical antipsychotics ranking highly as presumed iatrogenic causes of mortality (Moore et al., 2007c). Investigative journalists at the *New York Times* and *USA Today* searched the FAERS database in the context of the public debate on PBD and reported that paediatric deaths, where the presumed cause was an atypical antipsychotic, possibly numbered in the hundreds (Elias 2006; Harris, G 2008; Chapter 4.6.4). While not yet verified in formal research, these results are disturbing, and suggest further research into iatrogenic mortality is needed.

Implications for medical ethics

A further issue compounding the problems associated with the PBD phenomenon emerged from the US Senate Committee inquiry into financial relationships between the pharmaceutical industry and health care organisations and practitioners (Grassley, 2009). The Committee, led by Senator Charles Grassley (Republican Senator for Iowa), focused predominantly on the field of psychiatry. Several PBD researchers were named in Congress (Grassley, 2008), and in the media (Chapter 4.7). Specifically, the Congressional inquiry found a conflict of interest between some PBD researchers and the pharmaceutical industry that was providing substantial funding. This implied that this was a factor in the spread of the PBD diagnosis (Levin and Parry, 2011) (Appendix A15): the scientific method itself is compromised when researchers state that they need to call paediatric affect dysregulation "bipolar" in order to "get funding for our research" (Pavuluri, 2009; Chapter 4.8.2.20).

The four key principles of medical ethics are as follows:

1. respect for autonomy,
2. beneficence,
3. non-maleficence, and
4. justice.

Firstly, autonomy concerns the right of a patient to informed consent to treatment. In the case of children and young adolescents, parents or other guardians are responsible for making treatment decisions on the child's behalf. However, parents and guardians may have mixed motives when it comes to child behaviour problems. It is vital that the child's 'voice' is fully heard. The issue of iatrogenic harm and misdiagnosis, as described above, indicates that the second and third principles of non-maleficence ('first do no harm') and beneficence need to be closely examined in the case of PBD. The fourth medical ethical principle of justice concerns the right to equitable health care. Health care systems can fail to meet this principle if there are 'diagnostic up-coding' pressures, brief 'med check' appointments in psychiatry and paediatrics, and insurance companies favouring pharmacotherapy over individual, parenting and family therapy (Chapter 4.6.9; 9.3; 9.4.4).

Implications for psychiatric nosology

A stated goal of the DSM-III (APA, 1980) was to provide a reliable diagnostic classification system for clinicians and researchers, enabling them to ascribe the same diagnostic labels to the same phenomenological syndromes (p. 2). The fact that at the time schizophrenia rates in the US were double that of the UK and Europe was considered an embarrassment to pre-DSM-III psychiatric nosology (Kendell et al., 1971). The DSM-III introduction stated that it had specifically adopted the "descriptive approach" focusing on "clinical features of the disorders" and was deliberately "atheoretical with regard to aetiology" (p. 7). The descriptive approach has remained the basis of subsequent editions of the DSM.

The proposed PBD hypotheses were not included in either the 2000 revision of DSM-IV (DSM-IV-TR), or the latest edition (DSM-5) of the diagnostic manual. Nonetheless, the suggested diagnostic criteria for PBD followed the same descriptive psychiatry guidelines and were widely published and adopted into practice primarily within the US. The vastly higher diagnostic rates of PBD in the US compared with Europe and Australasia, which is over 100-fold higher for children and young adolescents (Clacey, Goldacre & James 2015), reveal a problem even greater than the international discrepancy over schizophrenia prior to DSM-III.

The critical implication for psychiatric nosology is that descriptive psychiatry alone, as exemplified in DSM and PBD diagnostic criteria, cannot provide reliability in either clinical practice or research. For this reason, a long-established view in psychiatric nosology, training

and clinical practice, has been to always apply the more comprehensive biopsychosocial model and individualised dynamic diagnostic case formulation approach. This approach should be combined with the assigning of DSM or ICD diagnostic labels for the following reasons: firstly, if past and present contextual factors are not considered, then a diagnostic label based solely on descriptive symptomatology may well be in error; and secondly, psychiatric symptoms need to be combined with a careful mental state examination. Accuracy in understanding the patient's history in context and assessing their mental state improves with knowledge of a patient in a therapeutic relationship gained over a number of sessions.

However, the realities of some health systems, particularly the US health system, undermine psychiatrists' capacity to fulfil these requirements: US psychiatrists have critiqued their health system for prioritising brief (15-minute) 'med check' appointments (Williams, 2008), and psychiatric training for being dominated by the descriptive approach that de-emphasises psychosocial factors and systemic case formulation (Tasman, 1999). In similar vein, PBD research has been criticized for over-reliance on symptom questionnaires (Carlson, 1998).

Another way of viewing this dilemma is to consider Eisenberg's comment: he suggested that psychiatry as a field demonstrates pendulum swings between 'brainless psychiatry' (where psychoanalytic or family systems perspectives at worst denied the presence of biological brain factors) and 'mindless psychiatry' (where symptoms are attributed purely to faulty brain biochemistry) (Eisenberg, 1986). It has been suggested that such 'mindless psychiatry', also referred to as 'biologism', has affected US psychiatry in recent decades more than any other jurisdiction (Silove, 1990), though similar pressures affect health systems globally. Further, it can be argued that the PBD phenomenon is emblematic of an era of 'mindless psychiatry' (Parry and Levin, 2012), a symptom of too superficial a psychiatric nosology.

A deeper critique of psychiatric nosology was encompassed in the 'anti-psychiatry' movement that flourished in the 1960s. That view is that descriptive psychiatry, embodied in the DSM, pathologises much of normality. Professor Thomas Szasz (State University of New York) argued that psychopathological symptoms were metaphors representing 'problems in living' that the sufferer was unable to communicate more directly. Szasz was basing this on a radical acceptance of the principles of psychoanalysis. In his book, "The Myth of Mental Illness" (Szasz, 1961), most would argue he went too far in denying the biological component of

mental disorders and that his implacable opposition to any form of involuntary treatment was unrealistic and unethical. However, Szasz is recognised as a key instigator of the reforms of psychiatry in the past half century. His criticism of the coercive aspects of psychiatry, particularly at the time, were important.

Szasz, along with others such as Kutchins and Kirk (1997) in their book "Making Us Crazy: DSM: The Psychiatric Bible and the Creation of Mental Disorders", argued against the medicalisation of 'problems of living'. Today, this critique has been most comprehensively argued by the British Psychological Society in its proposal of an alternative to symptom criteria-based psychiatric nosology: the Power-Threat-Meaning Framework (PTM-Framework) (Johnstone & Boyle, 2018). Within this framework, the narrative of meaning is constructed by the individual based on a wide array of contextual influences across the biopsychosocial spectrum and particularly in terms of "threat responses" that may manifest as "patterns in emotional distress, unusual experiences and troubled or troubling behaviour" (Johnstone & Boyle, 2018; p. 1). Perhaps no area of mental health deserves this kind of approach more than that of emotional distress and behaviour disturbance in children.

Outline of this thesis

Part I is an overview of the PBD phenomenon. It adopts a generally chronological historical perspective. It is lengthy but gives perhaps the most detailed narrative of the PBD era in the literature to date and illustrates both the need for the novel research that follows, as well as discussion of the issues concerning medical ethics and nosology contained in the PBD phenomenon.

Part II comprises the novel research of this thesis, structured in three chapters to examine the three research questions regarding: problems with research methodology in epidemiology; patterns of geographical 'spread' of the PBD hypothesis; and issues of lack of context in diagnosing PBD. Each of these chapters ends with a discussion of the findings.

Part III encompasses a broad discussion of the issues, where the PBD 'epidemic' is examined to attempt to understand the many factors that have led to it. The ethical and nosological implications are explored, as well as ideas regarding future research, and desired action.

The evolution of the PBD phenomenon has occurred over a quarter century to date: consequently, this thesis refers to a substantial amount of information. In addition to the thesis itself, there are several appendices attached: Appendix A comprises 36 published articles by this author and colleagues that relate to the PBD hypothesis; most have also been cited; Appendix B contains two tables of a timeline of key pro-PBD perspective articles and conference presentations and key sceptical perspective articles and conference presentations to provide a visual overview of the debate; Appendix C comprises three Word files (Appendices C1, C2, C3) that contain all the articles with abstracts that comprise the 835 articles used in Chapter 7. Each of these articles was assigned a 'perspective'; readers will be able to compare their own assessment of an article's perspective with what has been presented. This data is also available as online supplementary files with the published article (Parry et al., 2019b; Appendix A35). Additionally, there is a table of leading PBD authors (Appendix C4), a comparative table of pro-PBD versus sceptical/traditional articles by country (Appendix C5) and a narrative analysis of all non-US articles by country of origin (Appendix C6). Appendix D contains correspondence and several conflict of interest related items from pharmaceutical industry documents.

CHAPTER 1. DEFINING BIPOLAR DISORDER

In order to explore the validity of the proposed PBD hypothesis, it is necessary to ensure a clear understanding of the underlying premises of bipolar disorder itself. This chapter reviews the history of the defining of bipolar disorder, the debates about its boundaries, and the underlying problems from the perspective of psychiatric nosology in attempting to define any psychiatric disorder.

1.1 Brief history of bipolar disorder

States of manic excitement and melancholic depressive states have been described in the medical literature for centuries. However, the definitions and boundaries of what came to be called bipolar disorder have varied considerably over time. As Healy describes in his history of bipolar disorder (Healy, 2008a), in antiquity 'mania' was a broad term for insanity where there was some degree of physical overactivity or restlessness. In fact, most of the ancient clinical vignettes of "mania" were frequently the result of fever and would now be described as delirium (pp. 3-7). Also described in antiquity was "melancholia", literally "black bile" in ancient Greek, which was thought to make the body "cold and wet." Melancholia was often described by Hippocrates as also occurring in conjunction with febrile states, probably indicative of infection (p. 8). Another Greek physician, Aretaeus of Cappadocia, did use the term melancholia to describe severe depressive states (p. 10). Healy notes that early Roman writers used the term melancholia to indicate a "mild form of madness", with mania as a term for later and more severe stages (p. 11). Whether this is the same as modern concepts of bipolar disorder can only be a point of conjecture.

It was not until the 19th century that a disorder including the cycling of both manic and depressive episodes was really described. The French psychiatrists Jean-Pierre Falret and Jules Baillarger described disorders that overlapped in phenomenology, such as *folie circulaire*, *folie à double forme*, and *folie alterne*, which at least captured the idea of alternating manic and depressive episodes (pp. 56-63). In 1882 the German psychiatrist, Karl Kahlbaum described dysthymia and cyclothymia as representative of non-psychotic mood disorders, equivalent in today's terminology to unipolar depression and Bipolar-II disorder, involving a hypomanic or at least a non-psychotic manic episode (p. 64).

During the late 19th century, the term 'mania' was used to some degree similar to the way it had been in ancient Greece, as a general term for mental disorder. For example, at the time of the US census in 1880, there were "seven categories of mental disease: mania, melancholia, monomania, paresis, dementia, dipsomania, and epilepsy" (Kutchins and Kirk, 1997, p. 28).

Then in 1899 fellow German psychiatrist, Emil Kraepelin described "manic-depressive insanity" (Healy, p. 72). Kraepelin's findings are recorded in his seminal 1921 text *Manic Depressive Insanity and Paranoia* (Kraepelin, 1921). Kraepelin based his views on a meticulous examination of phenomenology and course of illness in 903 patients, using what later became a model for descriptive psychiatric nosology. However, Healy considers that part of Kraepelin's rationale with his construct of manic-depressive insanity was for it to act as "a foil" (p. 72) to his 1887 construct of 'dementia praecox' which later became better known as schizophrenia. The term 'schizophrenia' was coined by Eugene Bleuler in 1911 for non-affective psychoses, particularly characterised by loosened associations in thinking (Moskowitz and Heim, 2011). Kraepelin's emphasis was on the remitting nature of manic-depressive insanity as a comparison to the progressive impairment in dementia praecox. With both disorders, Kraepelin was describing severely ill hospitalized patients. Healy notes that Kraepelin could have used the term "'manic-melancholic disease', given that almost all the depressions he was faced with were melancholic in terms of their severity and clinical features" but that the term "depression" had recently come into vogue (Healy 2008, p. 76). On the other hand, Kraepelin also used manic-depressive insanity as almost a 'cover-all' term, stating he believed that even the "slightest colourings of mood, some of them periodic, some of them continuously morbid … represent manifestations of a single morbid process" (Mason et al., 2016, p. 3).

By the mid-20th century Eugene Bleuler and Adolph Meyer's separate but dove-tailing views had resulted in a clearer definition of schizophrenia, and in turn the classification of manic-depressive illness became more defined. In DSM-I (APA and CNS, 1952) "Manic Depressive Reaction" was categorized with the psychotic disorders, with three types: Manic, Depressed, and Other-Mixed. As Mason et al. (2016) note, "The manic type details what is most similar to the modern definition of mania: elation or irritability, with overtalkativeness, flight of ideas, and increased motor activity" (p. 3). DSM-II (APA, 1968) used the term "Manic-

Depressive Illness" and placed it within an "Affective psychoses" subcategory. DSM-III (1980) moved the disorder to the "Affective Disorders" category, then "Mood (Affective Disorders)" in DSM-III-R, and "Mood Disorders" in DSM-IV. In 2013, it received its own separate category of "Bipolar and Related Disorders" in DSM-5.

The features of a manic episode were given operational criteria in DSM-III, that included a sustained period of "elevated, expansive, or irritable mood" (p. 205) along with at least three (four if mood only irritable) out of seven of:

- increased activity
- pressure of speech
- flight of ideas
- inflated self-esteem
- decreased need for sleep
- distractibility
- excessive risk-taking activities

Further, the disturbance had to last at least seven days or require hospitalisation. Usually an episode would last several weeks to a few months.

The DSM-III described 'hypomania' as a "clinical syndrome that is similar to, but not as severe as, that described by the term 'mania'" (p. 207) and hypomanic episodes were classified as occurring in "Cyclothymic Disorder" (p. 208). The revised version of DSM-III (DSM-III-R; APA, 1987) in 1987 renamed classical Bipolar Disorder as Bipolar-I Disorder and added Bipolar-II Disorder, where hypomanic episodes lasting at least four days occurred interspersed with depressive episodes. This approach continued in DSM-IV (APA, 1994), around the time of the emergence of published research evidence for hypothesised PBD. The research presented cohorts of young children said to suffer from bipolar disorder, despite their symptomology not meeting the DSM-IV criteria for mania or hypomania, nor for major depressive episodes.

The ICD-10 criteria are somewhat stricter: either a single episode of mania must be accompanied at some time by an episode of major depression, or two episodes of mania are required for a diagnosis of Bipolar Disorder. Depressive syndromes vary in severity and type and are the more common of the two states. A major depressive episode must be present for at least two weeks.

1.2 **Debate over boundaries of bipolar disorder**

In recent decades debate over what constitutes bipolar disorder has increased. The term 'bipolar spectrum' has been coined. Proponents of a widened bipolar spectrum such as Professor Hagop Akiskal (University of California, San Diego), chief-editor of the *Journal of Affective Disorders*, argue for a spectrum involving: Bipolar-I (full mania); Bipolar-II (depression and hypomania); Bipolar-IIa (depression and cyclothymia); Bipolar-III (antidepressant triggered hypomania); Bipolar-IIIa (substance use triggered depression/hypomania); Bipolar-IV (hyperthymic temperament and depression); Bipolar-V (depression and dysphoric hypomania); Bipolar-VI (depression progressing to dementia) (Akiskal and Pinto, 1999, Akiskal et al., 2006, Ng et al., 2008).

Professor Emeritus Jules Angst (Zurich University, Switzerland), lead researcher of the "Bipolar Disorders: Improving Diagnosis, Guidance and Education" (BRIDGE) study, is another leading proponent of a widened bipolar spectrum (Angst, 2007). Angst and colleagues proposed that almost half the patients diagnosed with a major depressive episode in fact have a bipolar spectrum disorder (Angst et al., 2011). However, their article was critiqued in a letter to *Archives of General Psychiatry* for requiring no minimum duration of symptoms and having no exclusion criteria. Thus, any person with "an angry, agitated or elated response to environmental triggers or psychoactive substances" (p. 643), or patients with borderline-personality disorder or post-traumatic stress disorder (PTSD) or an agitated reaction to an antidepressant could all too easily meet the BRIDGE study group's definition of "bipolarity" (Allen et al., 2012; Appendix A21).

The DSM-III and subsequent editions, including DSM-5, have defined "rapid cycling" of episodes of bipolar disorder as "at least four mood episodes in the previous 12 months that meet criteria for manic, hypomanic or major depressive disorder" (APA Desk Reference DSM-5, 2013, p. 86). A sizeable group of psychiatrists, Akiskal and Angst among them, see this definition as too conservative: they also described ultradian cycling (Akiskal et al., 2000):

> Rapid-cycling patients lie along a spectrum based on the duration of episodes which, by definition, must meet the symptom severity thresholds for mania/hypomania and depression. Rapid (≥ 4/year), ultra-rapid (≥ 4/month) and ultradian (≥ 4 within a day) cycling patterns can be recognised clinically; they are

> distinguished from cyclothymic disorder which pursues a *subthreshold* course as far as symptoms (p. S16).

However, there are critics of the widened bipolar spectrum, notably Professor Joel Paris (McGill University, Montreal), who wrote "The bipolar spectrum: a critical perspective" (Paris, 2009). The article's abstract is a pithy critique of a widened bipolar spectrum:

> Recent suggestions to extend the boundaries of bipolar disorder to a broader spectrum lead to a concept of bipolarity different from that of classical psychiatry. It has been proposed that many patients with unipolar depression are actually bipolar and that many cases of substance abuse, personality disorders, and childhood behavioral disorders lie within the spectrum. However, since this expanded notion of bipolarity has been defined entirely on the basis of phenomenology, any expansion needs to meet broader criteria for validity. Bipolar spectrum disorders have a different phenomenology, family history, and course than classical bipolar disorders and do not respond in the same way to drugs. Until further research clarifies the boundaries of bipolarity, we should be conservative about extending its scope. (p. 206)

In an article titled "The medicalisation of 'ups and downs': the marketing of the new bipolar disorder", Professor Joanna Moncrieff (University College London) takes Paris' critique further by examining the social forces that led to the widened 'bipolar spectrum' (Moncrieff, 2014). She tracks how classically described manic-depression as "a rare and devastating condition" with episodes recognisable as "completely out of character" lasting weeks or months "mutated into something so vague and inclusive that the label can be attached to a whole myriad of common personal difficulties" (p. 582-583). Moncrieff lists research associated with pharmaceutical sponsors, and widely promoted internet-based tests, magazine quizzes and mood diaries as having popularised "modern-day bipolar disorder ... as on a continuum with ordinary character traits and everyday variability of mood and functioning" (p. 584). Moncrieff goes on to describe PBD as an extension of this push to widen the boundaries of bipolar disorder into the realm of 'everyday ups and downs' (p. 588-591).

Nonetheless, the DSM-5 has made some concession to those advocating a widened bipolar spectrum. In the official summary of the changes from DSM-IV-TR to DSM-5, the APA state (APA, 2013b):

> DSM-5 allows the specification of particular conditions for other specified bipolar and related disorder, including categorization for individuals with a past history of a major depressive disorder who meet all criteria for hypomania except the duration criterion (i.e., at least 4 consecutive days). A second condition constituting another specified bipolar and related disorder is that too few symptoms of hypomania are present to meet criteria for the full Bipolar II syndrome, although the duration is sufficient at 4 or more days. (p. 4)

While DSM-5 has to some extent tightened requirements for diagnosis with "an emphasis on activity and energy" changes, not just mood changes in mania ((APA), 2013b, p. 4), DSM-IV, DSM-5 and ICD-10 overall still reflect the predominant and long-standing view in psychiatry: episodes of mania and hypomania involve sustained mood and activity changes over a minimum of 7 or 4 days respectively.

1.3 **Prevalence of bipolar spectrum disorders**

Mania has classically been described as a relatively rare condition affecting less than 1% of the adult population. The WHO "Global burden of bipolar disorder in the year 2000" gave a prevalence rate of 0.49% and mean age of onset of 23-years-old (Ayuso-Mateos, 2006). The prevalence of bipolar disorder varies, depending on methodology and perspective of those deciding where to draw the cut-off for milder 'spectrum' cases.

An international survey, that incorporated subthreshold and spectrum cases, based on lay-administered interviews using the WHO Composite International Diagnostic Interview (CIDI), with 61,392 community adults across 11 countries, found the following DSM-IV lifetime rates: Bipolar-I disorder 0.6%; Bipolar-II disorder 0.4%; subthreshold bipolar disorder 1.4%. This gives a total 'bipolar spectrum disorder' lifetime prevalence of 2.4% (Merikangas et al., 2011). Of note in this study, the mean ages of onset (with rather narrow standard deviations) assessed by retrospective recall, were: Bipolar-I 18.4-years-old, (0.7); Bipolar-II 20.0-years-old (0.6); subthreshold bipolar disorder 21.0-years-old (0.4) (p. 6).

1.4 **Psychiatric nosology's blurred boundaries**

Unlike some other fields of medicine, diagnosis in psychiatry often involves a significant component of subjective evaluation. As Paris indicates, no matter how well defined

operationalised criteria may be in circumscribing a particular psychiatric disorder or syndrome, an underlying reality is that differing aetiologies, pathophysiological, normal physiological as well as psychological dynamics can underpin symptoms (Parry, 2009b, Parry, 2012a) (Appendices A9 & A20). This is particularly true for disorders that blend with normality such as generalised anxiety disorder and with the various NOS subcategories as in DSM-IV, or Other Specified/Unspecified and Related Disorders as in DSM-5.

Pathognomonic features are not abundant in psychiatry, but classical mania and melancholia have them: for example, highly pressured speech with rapid flight of ideas, or profound psychomotor retardation with anhedonia, respectively. In the absence of pathognomonic features and definitive laboratory tests, there will always be debate in psychiatric nosology about the boundaries of disorders. However, the debate regarding the diagnosis of bipolar disorder in the paediatric age range, particularly in pre-pubertal children, is one of the most contentious to date.

CHAPTER 2. CLASSICAL PERSPECTIVES ON MANIA IN CHILDREN

To understand why the PBD hypothesis that emerged in the mid-1990s in the US was a radical departure from the classical accepted view of early-onset cases of bipolar disorder, it is necessary to review the historical context. The PBD hypotheses of either ultradian-cycling mood lability or chronic irritability in young children were actually not new ideas, but they previously had never been accepted by the psychiatric mainstream. Kraepelin's views had laid the foundation for mainstream psychiatric nosology in the 20th century, and he had explored age of onset for manic-depressive insanity.

2.1 Kraepelin (1921) age of onset of manic-depressive insanity

Generally, the classical view in psychiatry seeing mania as having its peak onset in the late teens to early twenties was well expressed by Kraepelin in his study of 903 patients suffering from manic-depressive insanity. In his text, Kraepelin provides Figure 45 that shows the distribution of age of onset in 5-yearly intervals from age 10-years onwards (Kraepelin, 1921, p.168). Kraepelin's table is reproduced here as Figure 2.1. The findings outlined in this century-old table are consistent with the opinion that reigned during the 20th century and continues to do so in most child psychiatry jurisdictions. Kraepelin records that 0.4% of patients had their first episode by the age of 10 years, a further 2.5% between the ages of 10 and 15, another 16.4% by age 20, with a further 30.7% having first onset in their twenties.

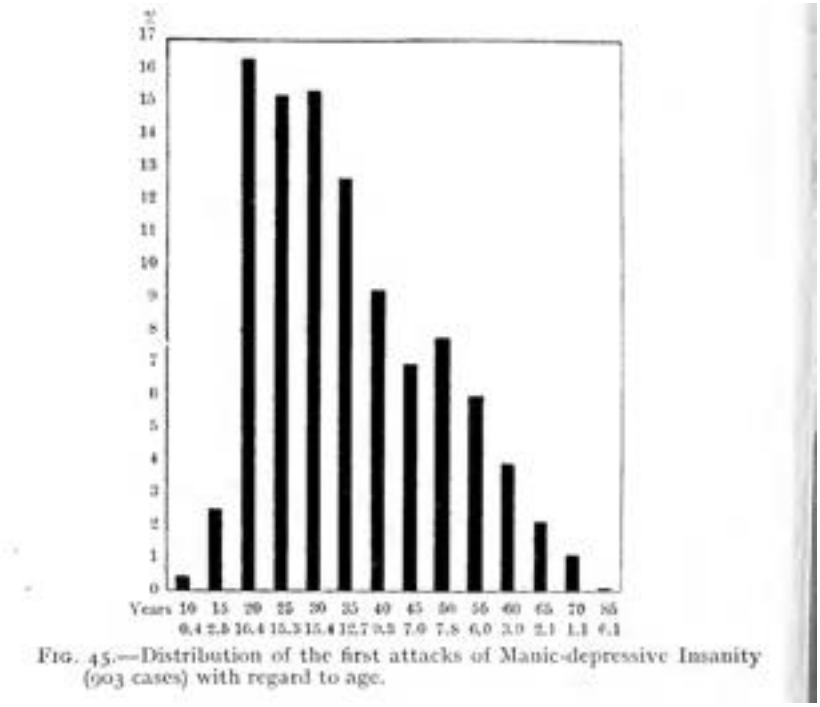

FIG. 45.—Distribution of the first attacks of Manic-depressive Insanity (903 cases) with regard to age.

Figure 2.1: Distribution of first attack of Manic-depressive insanity (903 cases) with regard to age (Kraepelin, 1921, p. 168)

Kraepelin also reported that 26% of episodes by age 15 were "melancholic" (p. 169), thus suggesting some of the 2.9% of cases by this age may not yet have had a manic/hypomanic episode. In noting the rarity of childhood cases, Kraepelin remarked that a colleague, "[Dr] Liebers, has described a case of mania lasting six months in a boy under five years of age" (p. 167): however, no further details are provided. What is clear from Kraepelin's research is that early adolescent onset was rare and pre-pubertal cases extremely exceptional.

2.2 Anthony and Scott's review of case reports to 1960

A comprehensive review of childhood cases in the literature to the end of the 1950s (Anthony and Scott, 1960) collected 28 articles from 1884 to 1954 that cumulatively reported on 63 cases, across 24 case reports and case series, with a further unspecified number of cases in four other articles. In assessing the validity of these reports, Anthony and Scott applied a rigorous set of criteria that included (italics in the original): "evidence of an abnormal psychiatric state … approximating to the *classical clinical description* as given by Kraepelin, Bleuler, Meyer and others"; "evidence of a 'positive' family history" of manic-depressive psychosis; "evidence of an *endogenous* illness indicating the phases of the illness alternate

with minimal reference to environmental events"; "evidence of a *severe* illness as indicated by need for in-patient treatment, heavy sedation and E.C.T."; "an *absence* of features… of schizophrenia, organic states etc."; and "evidence of *current*, not retrospective assessments." On this basis, they concluded that only "… three cases (who) were all 11 years of age … showed alternation of mania with depression. All other cases were open to the charge of misdiagnosis" (p. 58).

The review reported Kraepelin's findings and two other clinical prevalence studies: Strecker's (1921) findings, who "in his review of 5000 consecutive admissions, picked up ten cases starting below the age of 15." All cases were at least 10 years old and only one was clearly manic, the others presented depressive syndromes. In the original article, Strecker gives the "age of incidence in the manic-depressive group as follows: one at ten, three at twelve, one at thirteen and five at fourteen" (Strecker, 1921). Strecker does not say which case was the "frankly manic" one, but he does note that the 18 cases of 10 manic-depressive, four uncertain and four of dementia praecox (ages 11-14 years) amounted to "less than one half of one percent of the [psychiatric] admission rate" (p. 209) for the particular paediatric hospital in Philadelphia, US. With only one case of definitive mania in that under-15-years cohort, the clinical prevalence rate was 0.02%.

In contrast, Anthony and Scott also cite Barrett (1931), who, in "investigating 100 cases that occurred before the age of 20, found that five had their onset before the age of 12" (p. 56). Barrett, in his original article, reports on these five cases in detail. Three had strong family histories of manic-depressive psychosis, while family history was unknown in one case. All were followed up into their late teens, and convincing descriptions of mania were described in three cases; the other two had only severe depressive episodes. The age of first manic or depressive episode was after age 10 in the three cases which exhibited mania: four months of fortnightly cycling of mania and depression following seven months of depression starting at age 10-years; a manic episode at age 15-years following severe depressive episodes from age 11-years; and a manic episode at age 18-years. A fourth case gave a history of a prior 4-day hypomanic episode at age 10-years (Barrett, 1931). Once again these are peri-pubertal children and young adolescents, not very young children. Barrett does not describe the other 95 cases with onset prior to age 20-years.

Anthony and Scott made several observations that show the PBD hypothesis was not new. They reported "fashions in diagnosis" (p. 60) starting with a 19th century view among some early psychiatrists (predating the subspecialty of child and adolescent psychiatry) of not distinguishing between childhood and adult phenomenology, which could lead to misdiagnosis. In particular, they refer to late 19th century psychiatrists: Mills (1888), who "insisted that all forms of adult psychoses existed in childhood and that mania was one most frequently seen"; Down (1887), who described several cases of "infantile mania"; and Fletcher (1895), who had described "maniacal states in children which he attributed to the stresses of school life!" (p. 60).

In short, the authors concurred with the early 20th century view as exemplified by Kraepelin (1921), Strecker (1921), Barrett (1931) and Kasanin (1931), that manic-depressive psychosis may have been extremely rare in presenting an early-onset around puberty, in the 10-15 years age range. In the 1930s some authors were searching for "pre-psychotic personality" traits that may be harbingers of later "affective psychoses," but the cases described had been critiqued as either simply unlikely to be manic-depressive or "more likely due to organic disturbances such as toxic states" (p. 60). The 1940s and 1950s had some further reports of child cases from both the "clinical" (biomedical) perspective based on phenomenology, as well as the psychoanalytic perspective, echoing Melanie Klein's developmental theories. Anthony and Scott note that a strong challenge to both these theories of biomedical and psychoanalytic pre-pubertal onset came from prominent psychiatrists, citing Kanner (1937 and later textbooks), Bradley (1945) and Lurie and Lurie (1950) in particular, who disputed the existence of childhood onset (p. 60).

McHarg (1954) commented on the unusualness of pre-pubertal onset in a case report of an 11-year-old girl who presented with a classical 8-week-episode of florid mania, followed by a similar length depressive episode and then full recovery, a year before her menarche. He also reviewed the literature to that time and corroborated the findings of Anthony and Scott (1960). McHarg noted: "In the literature, there are practically no detailed accounts of manic states in the pre-pubertal period" (p. 535).

Anthony and Scott also described confusion due to a lack of consistency regarding the term 'children': suggestions had been made to limit this term to "those of 12 years and under" (p.

53). However, they preferred a "further delimitation of 'childhood proper' to be the period before the appearance of any secondary sexual characteristics" (p. 53) and were of the opinion that the onset of puberty marked the beginning of risk for manifestation of the illness. They stated they were "supporters" of the "late childhood" as "early onset" group of researchers such as Kraepelin, who defined the illness, and Kanner, who was chief-editor of one of the most prominent textbooks of child psychiatry (p. 60).

This was then the dominant view within child psychiatry in the mid-20th century and continued until the mid-1990s in the US, and as diagnostic rates indicate (Chapter 4.8.6.14), continues to be the dominant view in the UK, several European nations and Australia and New Zealand (Clacey et al, 2015; Goetz et al., 2015; Kessing et al., 2014; Sourander, 2004).

2.3 Glovinsky's 2002 review: History of childhood-onset bipolar disorder to 1980

Nearly a half-century later, Glovinsky also produced an historical review. It was, however, more favourable to the PBD hypothesis (Glovinsky, 2002). Writing in the US during the PBD era, he cited four very early case reports. The first was an 18th century case of "mania in an infant," but he noted "the case has a strikingly organic quality" and the description was more in line with a delirium from which the infant died (p. 449). A second case, reported by Haslam (1809), was of a 10-year-old boy who had been "violent, cruel, destructive – an unrelenting foe to all china, glass, and crockery" (p. 449,) though this may simply be a description of a possible CD. A third early case cited in Glovinsky's review was from Crichton-Browne (1860), who reported "melancholia and mania in the 'early life of the child'". Crichton-Browne is reported as commenting that "… the disease appears incompatible with early life" (p. 449) before going on to state that mania "may occur in infancy and childhood" (p. 450). However, the descriptions provided again could be ascribed to delirium or other organic brain disorders, as he also states that such mania is "often accompanied by bodily disease" (p. 450). In contrast, a fourth cited early case report [Beach, 1898] is of a 13-year-old boy diagnosed with *folie cirulaire*:

> He was a dull child, and had been so often punished at school, on account of his slow progress, that he became deeply melancholy and tried to kill himself. The

> melancholy alternated with mania, in which he whistled and sang all day and night, tore his clothes and was filthy at his habits. (p. 450).

The description is suggestive but not definitive of bipolar disorder: a boy with learning disorder subject to frequent punishments, and entrapped in a situation of unachievable expectations, is likely to react with emotional and behavioural dysregulation.

In regard to early childhood onset, Glovinsky (2002) noted that "Kraepelin referred to the possibility of manic depression occurring in early childhood, although he saw this disorder as extremely rare" (p. 450), and also cites a German contemporary of Kraepelin, Theodor Ziehen, who asserted that a "simple, non-recurring mania occurs only exceptionally during childhood" (p. 450). The description Ziehen gives is certainly compatible with classical mania. The episode has a sudden onset and lasts days to months. However, it is quite atypical that Ziehen describes these 'exceptional' cases as non-recurrent and that "almost all cases can be cured" (p. 451). Glovinsky also referred to Leo Kanner, describing manic and depressive reactions in young children in his seminal 1935 textbook *Child Psychiatry*, but that there was "subsequent silence" on the issue in later editions probably reflecting the "resistance to the diagnosis of manic depression in early childhood and the influence of psychoanalytic theory" (p. 452). However, Glovinsky doesn't repeat what Anthony and Scott (1960) say about Kanner being adamantly opposed to the concept of bipolar disorder occurring in childhood. Glovinsky disagreed with Anthony and Scott's review, stating: "By setting up their own criteria, Anthony and Scott essentially swept away the concept of manic depression in children" (p. 454).

Illustrating there was indeed debate in the mid-20th century, Glovinsky quotes from a review of "psychoses in children" by Bradley (1945), and an 18-case series of "manic-depressive psychoses in children" by Campbell (1952). Bradley (1945) had concluded:

> In children, sustained elevation of mood and exhilaration are not encountered except in response to reasonably appropriate stimuli. Hyperactivity is a frequent symptom of conflict in children but not observed in attacks that are reminiscent of adult mania… it is likely the rare reported cases of manic psychoses in children … have been confusion (p. 452)

In contrast, Glovinsky reports Campbell (1952) describing mainly cyclothymia in children and adolescence with a familial history of manic-depression. Glovinsky quotes Campbell "from his

research with manic-depressive children and adolescents" as concluding "over-emphasis has been placed on conventional and dynamic factors in the psychiatric illness of children" (p. 453). Campbell's original 1952 case series did indeed advocate for greater recognition of childhood onset of manic-depressive psychosis and cyclothymia. After reviewing the scant literature, Campbell (1952) stated:

> It is unfortunate that the reported cases of manic-depressive psychosis in children are presented as if they were unique, or unusual, because, when the criteria for this entity was established, the present writer collected 18 cases from his own practice within a four-year period (p. 425).

However, Campbell's 18 cases included only six that had "manic reactions," the rest all had "depressive reactions" as Campbell was of the school that classified unipolar depressive episodes as part of manic-depressive illness. The six "children" were in fact all adolescents. A major depressive episode had preceded the manic reactions in all but one case. The critical age of onset of hypomania/mania was (with age of first depressive illness) were: 14 (13); 15 (14); 15; 18 (16); between 14 and 18 (14); and 19 (14) (Campbell, 1952). This case series is remarkable for so many cases from the one clinician, however Campbell appears to have specialised in treating adults with bipolar disorder, and many cases were their offspring. In terms of the classical view of mid-adolescent onset, Campbell's findings are not unremarkable. Glovinsky, writing in 2002 in the US at the height of the PBD phenomenon in that country, interpreted Campbell's case series as indicative of pre-pubertal children, when it was in fact of adolescents who were mostly high-risk offspring of parents with classical manic-depressive psychosis.

Campbell also cites Kanner in his seminal textbook, 1946 edition, as saying: "manic-depressive psychosis is so rare below the age of 15 or 16 that it is *negligible*" (italics in Campbell's original) (p. 425).

In summary, the debate over whether mania occurs in childhood is not new. However, the early published literature, such as it is, established the majority view in psychiatry in history. This view was of bipolar disorder having a peak onset in late adolescence to adulthood with rare peri-pubertal and early adolescent cases, and pre-pubertal cases being exceedingly rare, verging on non-existent.

2.4 Historical international epidemiology

The classical view of a relatively non-existent prevalence rate, exemplified in Kraepelin's research, is also reflected in international clinical prevalence research prior to the late 1990s. Beginning with the UK, the results of some of the most significant studies follow.

A British 1952 review of 2,200 clinical paediatric psychiatric cases found only two cases of teens with manic-depression (Barton-Hall, 1952), a clinical prevalence rate of 0.09%. A later retrospective review of clinical paediatric psychiatric patients at the Maudsley Hospital in London identified only 38 cases of ICD-10 bipolar disorder over a period of 22 years (1974–1996). The mean age was 14.2 years with an age range of 11-18 years (Sigurdsson et al., 1999).

In New Zealand (NZ), a 20-year follow-up study (Werry et al., 1991, Werry and McClellan, 1992) examined all inpatient admissions to the child and adolescent psychiatric ward in a catchment area of 1 million people. Fifty-nine children under age 18 presented with a confirmed psychotic illness that included schizophrenia, schizoaffective disorder or mania/bipolar disorder. Age of diagnosis was based on reports of first symptoms, not date of admission. Only three were aged 12 or under at onset of symptoms. Of these, the youngest was reported to have had their first manic episode at age 9 and only aged 7 at onset of first symptoms, but later was diagnosed with schizophrenia.

In Denmark, comprehensive national hospital records indicated only 39 cases (1.2%) of psychiatrically hospitalised children aged 15-years-and-under between 1970-86 were diagnosed with mania or bipolar disorder (Thomsen et al., 1992). A Finnish survey of 64 of the nation's 69 paediatric psychiatric inpatient units in January 2000 found 504 children and adolescents (mean age ±SD: boys 11.4 ±3.7 years, range 2-18; girls 13.9 ±2.9 years, range 5-18) and only eight with a diagnosis of bipolar disorder (age not specified), a rate in this high acuity clinical population of just 1.6% (Sourander, 2004). An earlier survey in 1994 (Räsänen, et al., 1998) calculated against community population figures found a low community prevalence rate of only 1.7 cases/100,000 (0.0006%) first-episode hospitalised cases of mania per year for those aged under 20 years. In the US, there appear to have been no clinical epidemiological studies of bipolar disorder in the paediatric age group prior to the 1990s, but community-based studies were undertaken.

The twelve most applicable community epidemiological studies (six US, six international), of mainly adolescents, were reported in a meta-analysis (Van Meter, Moreira & Youngstrom 2011). The authors reported that PBD occurred with a community prevalence of 1.8% around the world. However, a later critique of this meta-analysis demonstrated much more conservative findings from the original twelve studies (Parry, Allison & Bastiampillai 2018a; Appendix A31; Chapter 6). Where both parent and adolescent questionnaire reports were required to meet diagnostic threshold, rates of bipolar disorder in the community samples fell close to zero.

By way of example, to mention just one of these studies, the Great Smoky Mountains Study of four thousand five hundred 9 – 13-year-olds in the Appalachian region of the US, completed in 1994, found no cases of mania and a 0.1% 3-month prevalence of hypomania, whilst anxiety disorders were 5.7%, CD 3.3%, oppositional defiant disorder (ODD) 2.7% and hyperactivity 1.9%: all reflective of accepted rates of such disorders (Costello et al. 1996).

2.5 Perspectives on childhood emotional and behavioural dysregulation

2.5.1 Classical psychoanalytic interpretation of childhood mania

It is important to comment on classical psychoanalytic, contextual and developmental theories of childhood emotional and behavioural disorders, which sought to explain such phenomenology without recourse to alternate ideas of 'bipolarity'. PBD researchers claimed, in contradiction to the classical perspective, that childhood mania is not uncommon. Further, some proposed a revisionist view of history where childhood mania had always been relatively common and overlooked. A particularly early case sometimes cited (Jairam 2007) is a mid-19th century case report by the French psychiatrist Jean-Etienne Esquirol. He reported a case of an 8-year-old Parisian boy with alleged mania. Jairam's article noting this historical case was a counterpoint commentary to the first article in *Australasian Psychiatry* about the PBD diagnosis originating in the US (Parry & Allison 2008) (Appendices A2 & A3). However, Esquirol's actual description of the case is transcribed by Healy in a letter to the editor response (Healy 2008b) to Jairam's commentary. Healy noted that Esquirol did not use the term 'mania', which at the time referred more generally to insanity than its current usage,

but rather simply listed the case under a section headed "*Folie*", an even more generic term for mental distress.

The psychoanalytic concept of the 'manic defence' as a psychological manoeuvre to manage mental distress has long been a cornerstone of psychodynamic psychiatry and psychology. This term dates mainly to the work of Melanie Klein, and although her description of it was steeped in the rather archaic psychosexual Freudian model of development, she makes it clear that a small child and an adult both use manic defences of increased activity, grandiosity, ebullient mood and aggressiveness against feeling small, threatened or demoralised and in order to gain a sense of control in their lives. As Klein puts it, the manic defence is the "utilisation of the sense of omnipotence for the purpose of controlling and mastering objects" (Klein, M 1935). It is normal development in the 'terrible twos' for young children to enact manic defences while interacting with their parents. Considering this, all that Esquirol records is:

> In 1814, I took over the care of an 8 year old child. The child was physically healthy and had normal cognitive function. He had been frightened badly by his governess during the siege of Paris. A lot of what he had to say was appropriate. But nothing could restrain him. He frequently ran away from his mother and governess and wandered around the city. He often went down into the court of the hotel and ordered a team of horses, pretending to be the master. He would claim confidently that he had won a large sum of money in the lottery. If he passes by a stall, or a shop, he might grab the money his mother or other customers had paid for their purchases. He often insults, provokes, or strikes people he meets, especially those visiting his mother. As soon as he sits down anywhere he falls asleep. When he wakes up, he creates pandemonium. He regularly abuses his mother and is unwilling to do anything she asks. (Healy 2008b, p. 295)

Esquirol described this case during the Napoleonic wars. It would appear the boy could easily have been displaying distressed behaviour, including manic-defence behaviour, as part of a trauma-induced stress disorder.

2.5.2 **Piaget's pre-operational stage and imaginative responses**

Prominent as well in developmental psychology are Piaget's theories of cognitive development (Ginsburg & Opper 1987). Piaget conceptualised 2 – 7-year-old children as being in a stage of "pre-operational thought" characterised by "pre-causal logic" and rigid, egocentric and animistic magical thinking (p. 67). Thus, pre-school and many junior primary school-aged children hold beliefs in such things as the Easter Bunny, Father Christmas, Jack Frost and the Tooth Fairy. Under stress, such recourse to pre-causal fantasy increases as the child defends against psychodynamic, family dynamic and social stressors upon his/her psyche. For a child, egocentric grandiose ideas can help balance his/her sense of smallness and vulnerability.

Esquirol's 8-year-old boy in Napoleonic Paris could be seen as utilising such imaginative ego-defences in reaction to the traumas in his life as well as acting out the anger, fear and traumatic memories of his real-life experiences. This account raises more questions than answers: for example, what had been the context of his and his family's experiences during the Napoleonic wars? Traditional child psychiatry would approach Esquirol's 8-year-old boy from a biopsychosocial developmental and contextually meaningful perspective, not assume a manic episode on the inference from reported behaviours.

2.5.3 **Evolutionary psychology and responses to developmental trauma**

The first published scientific reference to the 'fight/flight' response dates from 1915 (Cannon 1915) and the understanding of stress responses has progressed markedly in recent decades. Evolutionary psychology, utilising more neuroscientific versions of the above described ego defences, would say it is normal for higher mammals to engage in the full repertoire of survival responses that are referred to as 'fight', 'flight', 'freeze', and 'appease' (Cantor & Price 2007), and in the face of overwhelming danger they may dissociate into a state of "feigning death, vasovagal syncope, and behavioural shutdown" (Porges 2009, p. S88). The psychoanalytic term of 'manic defence' can be seen in the 'appeasement' strategy of mammals, which seeks to socially engage a more powerful other in a less threatening mode of relating. Another mode is "somatic re-enactment" of experienced trauma and abuse in play, where a child may enact either perpetrator or victim behaviours (Norton, Ferriegel & Norton 2011).

Schauer and Elbert (2010) describe a "defensive cascade" of six stages of dissociative survival response to threat and trauma: "*Freeze, Flight, Fight, Fright, Flag,* and eventually *Faint*" (p. 111). An initial freeze response (attentive immobility) to threat may be followed by sympathetic 'uproar' reactions of flight or fight, thereafter possibly by parasympathetic 'shut-down' reactions of fright (tonic immobility), flag and faint (p. 111): various responses can be triggered by cues in simple or complex PTSD. Human children are especially adept at employing this range of behaviours with intensity when they feel threatened (Perry et al. 1995). Esquirol's 8-year-old boy could also be conceptualised as moving through a range of the so called 'F-responses' to trauma and triggering cues.

2.5.4 **Disturbances of attachment**

Children's resilience to trauma is buffered by the sense of safety and security they feel in their relationships with parents. Young children in war and natural disaster zones are more likely to develop PTSD and other psychopathology if they have an insecure attachment with caregivers (Punamaki et al. 2015). Esquirol alludes to attachment insecurity for the young Parisian boy: that he had been "frightened badly by his governess during the Siege of Paris." Relational context for any social species is vital for dealing with stress. Denton in an editorial in the *American Journal of Psychiatry* focused on "relational diagnosis" as a necessary corrective to a "deficiency" in the DSM, and that "we are hard-wired for attachment" (Denton 2007).

Attachment theory is a bedrock theory of modern developmental psychology and child and adolescent psychiatry. It provides contemporary theoretical underpinnings for psychotherapy (Holmes 2017) and assists in understanding the response to trauma, particularly developmental trauma (Glaser 2000). It owes its origins to the pioneering research of British psychiatrist and psychoanalyst John Bowlby, who published his 3-volume opus between 1969 and 1980 (Bowlby 1969-1973-1980).

Bowlby constructed his theory from combining his psychoanalytic insights with findings in ethology about the nature of bonding in social species, and observational studies of orphans and hospitalised children. Ainsworth et al., in research of parent-child dyads using the 'Strange Situation Procedure', categorised three patterns: 'Type B' – securely attached children with attuned parents/attachment figures; 'Type A' – avoidant children with

dismissive parents/attachment figures; 'Type C' – clingy children with enmeshed parents/attachment figures (Ainsworth et al. 1978). The theory has been expanded upon by researchers such as Crittenden who have refined the concept and description of secure and insecure attachment patterns, as adaptive responses to contextual stressors past and current (Crittenden & Heller 2017).

Attachment theory has much to say about the purpose of apparent dysregulation of emotion and behaviour, especially in children who are insecure in their attachments. Paul Dignam, Michael Berk and I authored a review of an understanding of psychopathology through the lens of attachment theory (Dignam, Parry & Berk 2010; Appendix A12), where we noted the following with respect to the PBD hypothesis:

> 'Antisocial' behaviour is normative for toddlers. Impulsivity and emotional volatility are characteristic of all children, and especially so of those from disrupted backgrounds. Children who cannot access a secure attachment figure to foster emotional self-regulation develop other strategies. Severely insecure-avoidant children (Crittenden's 'Compulsive As') inhibit negative affect until they explode. Severely insecure-ambivalent children ('Coercive Cs') exaggerate negative affect to coerce marginal caregivers into providing what they need, oscillating widely from furious rage to pathetic helplessness. Both sorts of children can find themselves anergic, lowered in arousal, 'depressed'; both can be raging, destructive demons, 'high'. An explanation of the developmental story, and observation of dyadic behaviour can provide a strategic understanding of the behaviour from which appropriate psychotherapy can evolve (p. 205).

2.6 **Concluding comments**

While these explanations have been addressed here only briefly, it is critical to note that there is a vast literature on emotional and behavioural dysregulation as maladaptive chronic survival mechanisms in response to insecure attachment and trauma, particularly developmental trauma that is not buffered by attuned carers. Such dysregulation by its nature is context dependent and will 'cycle' several times a day: in other words, in an 'ultradian' pattern. Furthermore, chronic hypervigilance can manifest as chronic irritability. These psychodynamic, developmental and stress response perspectives of emotional and

behavioural dysregulation were weakly considered, if at all, in the PBD research that ensued from the mid-1990s (Parry 2012f; Appendix A19). They were also apparently not considered in the presentation of descriptions of infant and toddler tantrums given to parents via the website of the Child and Adolescent Bipolar Foundation (CABF) (Chapter 4.3.3) and in children's story books like *Brandon and the Bipolar Bear* and *My Bipolar Roller Coaster Feelings Book* (Chapter 4.3.4). In such material for parents and children, normal childhood responses of sadness, anxiety-driven fantasies, exuberance, frustration and rage at being denied something could all be relabelled as ultradian cycles of pathological bipolar mood swings. If greater consideration had been given to these aids in understanding and assessing an individual, then the PBD hypothesis may not have evolved as it did.

CHAPTER 3. THE ORIGINS OF THE PROPOSED PBD DIAGNOSIS

The PBD hypothesis was a marked departure from mainstream psychiatric theory and practice. The use of psychotropic medication designed for treating adult bipolar disorder in such young children became a matter of concern. This chapter outlines the development of the two phenotypes, so as to enable the reader to follow the complexities of the PBD epidemic as documented in Chapter 4.

3.1 Late 20th century calls to consider paediatric variants of mania

Having now examined both historical reviews and international epidemiology of evidence regarding bipolar disorder in children through to the start of the 1990s, it is clear that extraordinarily few substantiated instances of pre-pubertal cases had ever been reported. The classical view has been soundly based on this. However, despite the weight of evidence of the decades of reporting outlined in the previous chapter, from time to time different authors had suggested a higher rate of prevalence in children. This again became a topic of debate in the latter part of the 20th Century.

Glovinsky, in the review previously discussed, that was published in 2002, some seven years after the seminal PBD hypothesis articles, outlined three case reports to support the existence of childhood bipolar disorder. In a section titled “revival of the concept of manic depression in children,” he cites the following: Feinstein and Wolpert in 1975 report a 5-year-old girl who was allegedly manic since age of 3-years “presenting with hyperactive behaviour, low frustration tolerance, impulsivity, destructiveness, and inability to concentrate … subject to rapid mood shifts”; Thompson and Schindler in 1976 described a 5-year-old displaying ‘embryonic mania’ where “there were internal fantasies with manic-depressive qualities, including heightened self-esteem and thoughts of omnipotence that were not of psychotic proportions” with subsequent acting out behaviours; LaGrone in 1981 described “a child of 11.5-months whose behaviour pattern was suggestive of early-onset bipolar disorder” based on “hyperactivity, sleeplessness, and extreme irritability” in a family where mother had a history of depression, and the father of aggression and high energy levels (pp. 454-455).

Glovinsky also made reference to the work of DeLong (1983, 1990) for the use of lithium for treatment of “hyper-aggressive behaviours” in children who had “some symptoms of manic depression but had not been diagnosed as such” (p. 455). A focus on irritability, and the term “affective storms” was also used in “an important paper published by Davis (1979) in which he described a ‘manic-depressive variant syndrome of childhood’” (p. 455). Despite citing only these three cases from the 70’s to the 80’s, Glovinsky’s historical review concluded: “By the beginning of the 1980s it was increasingly accepted that young children could present bipolar symptomatology” (p. 456). He further cited a 1983 book chapter of New York child psychiatrist, Gabrielle Carlson (Carlson 1983).

Carlson became a leading figure in US child psychiatry, and as of 2017 is president-elect of the American Academy of Child and Adolescent Psychiatry (AACAP). She suggested that mania may present differently in pre-pubertal children and young adolescents (Carlson 1983), and pre-pubertal mania may be atypical and present with hyperactivity and lack of discrete episodes. Carlson and Weintraub (1993) again raised the question in an article titled “Childhood behavioural problems and bipolar disorder – relationship or coincidence?” They reported a relationship between childhood externalising disorders (ADHD and conduct problems) and having a parent with bipolar disorder. However, follow-up of these children showed young adulthood psychopathology but no greater risk of bipolar disorder, the authors called for further research. Later, Carlson was to become one of the prominent critics of the PBD epidemic that erupted in the US.

3.2 Introduction of two PBD hypotheses

In the mid-1990s two US academic child psychiatric centres independently defined ‘juvenile’ versions of bipolar disorder: the Washington University in St Louis (WUSL) group in 1994 (Geller, Fox & Clark 1994) and the Massachusetts General Hospital, a division of Harvard University (MGH-Harvard) group in 1995 (Wozniak, Biederman, Kiely, et al. 1995). The two versions of juvenile mania received significant acknowledgment through being published in *JAACAP*, the flagship journal of AACAP.

3.2.1 **The ultradian cycling PBD hypothesis**

Geller and colleagues in Missouri further clarified their definition of childhood cases of bipolar disorder as exhibiting "ultra-rapid" (more than four times per month) and "ultradian" (more than four times per day) cycling of mood episodes in an article the subsequent year in the *Journal of Affective Disorders* (Geller et al. 1995). While classical bipolar mood changes in adults are generally considered 'rapid' if they occur more than 4 times per year, Geller et al. proposed that in children, an episode of elevated, irritable or depressed mood was seen as indicative of PBD if it lasted at least 4 hours. They further suggested that several such episodes would occur per day, hence the term 'ultradian' cycling: over 80% of Geller et al.'s cohort of 115 children and early teens were ultradian cyclers (Geller et al. 1995). In a follow-up article in 2008, Geller et al. reported on this cohort, to a mean age of 18-years, 8 years later. With a 94% retention of subjects of whom 44% still met the research criteria for bipolar disorder, 67% of this group were reported as still exhibiting ultradian cycling (Geller et al. 2008). Indicative of the prominence of PBD by the mid-2000s in the US, this follow-up research article was published in the 'high impact factor' journal *Archives of General Psychiatry.* The chief-editor rated it as one of the most influential articles of that year, and the journal's website listed it as the most downloaded article of 2008 (Chapter 4.8.2.15).

Geller and colleagues further proposed that manic symptoms would be constrained by developmental age. In 1997 Geller and her WUSL colleague Luby were authors of the first '10-year review' of PBD (again, published in *JAACAP),* and examples were given of such constraints on presenting features of mania: elevated mood may be deduced from "a happy child laughing in the office in the context of a miserable history (e.g. school suspensions, family fights)" (p. 1169); grandiose delusions by "a manic adolescent, even in the absence of musical talent or ability to carry a tune, might practice all day with the belief he or she can become a rock star"; and hypersexuality when "adolescents develop romantic fantasies and delusions about teachers" (p. 1170; (Geller & Luby 1997)). This prominent review article in *JAACAP* emphasised the proposed pre-pubertal and ultradian aspects of the disorder:

> Pre-pubertal onset manic-depressive disorder ... may present ... with continuous, mixed manic, rapid-cycling of multiple brief episodes ... Thus, children may be having a laughing fit and happily doing arts and craft when, without any environmental prompt, they suddenly become miserable and acutely suicidal ...

parents describe their children rapidly cycle sometimes numerous times a day (p. 1172).

3.2.2 Chronic irritability as a PBD hypothesis

While the WUSL group proposed rapidly cycling elevated and dysphoric moods as a defining criteria in their PBD hypothesis, the MGH-Harvard group in Boston hypothesised that "the course of childhood-onset bipolar disorder tends to be chronic and continuous rather than episodic and acute, as is characteristic of the adult disorder" (Biederman et al. 1996, p. 998). They described episodes lasting years characterised by severe irritability and "affective storms" that were "seldom characterised by euphoric mood" (Wozniak, Biederman, Kiely, et al. 1995, p. 872). According to Biederman et al., the mean age of onset of in their study was 4.4-years-old; 23% had manic symptoms in the first year after birth; the mean duration of episode was 3 years, implying the syndrome was quite pervasive for the cohort of 7.9-year-old children. They claimed the disorder was common, affecting 16% of their clinic-referred children, and 98% of the children had comorbid ADHD (Wozniak, Biederman, Kiely, et al. 1995). The "type of irritability observed… was very severe and often associated with violence" (Wozniak, Biederman, Kiely, et al. 1995, p. 872). The implications of defining mania in this way were critical: many children formerly diagnosed with the DSM disruptive mood disorders (ADHD, ODD, or CD) could be diagnosed as having comorbid PBD if their mood was irritable. Further, most of these children described by Biederman and colleagues did not have elevated mood, contrary to the variant of PBD described by the WUSL group.

3.2.3 From hypotheses to phenotypes

In Geller and Luby's first *JAACAP* '10-year review' (1997), they had primarily referred to their ultradian cycling hypothesis of PBD. However, they did cite the work of Biederman and his colleagues, particularly regarding the high comorbidity of PBD with ADHD. The second *JAACAP* '10-year review' of PBD, came 8 years later (Pavuluri, Birmaher & Naylor 2005), and described both versions of PBD, coining the terms 'narrow phenotype' and 'broad phenotype' for the two PBD hypotheses.

The review was ambiguous in its definition of 'narrow phenotype' PBD. Pavuluri et al. noted that a "roundtable on pre-pubertal bipolar disorder" hosted by the US National Institute of Mental Health (NIMH) had used the term 'narrow phenotype' PBD to apply to children fitting

the DSM-IV criteria for Bipolar-I or Bipolar-II disorder (p. 846). However, the article's content appears to have conflated this with the WUSL group's rapid-cycling cohort PBD, who by having episodes less than the required 4 days (hypomania) to 7 days (mania) duration technically met DSM-IV criteria for Bipolar-NOS, not Bipolar-I or Bipolar-II (p. 847). The key point that this *JAACAP* second '10-year review' article made was that the 'narrow phenotype' pre-pubertal children were displaying elevated mood symptoms. Pavuluri et al. distinguished this 'narrow' phenotype from the MGH-Harvard group's description of chronically irritable cohorts, that was categorized as 'broad phenotype' PBD. They noted that: "the 'broad' phenotype constitutes the majority of the referrals to clinicians and present with severe irritability, "affective storms," mood lability, severe temper outbursts, poor concentration, and impulsivity with or without clear episodicity (Biederman et al. 1996)" (p. 847). This second *JAACAP* '10-year review' did note that this 'broad phenotype' of childhood bipolar disorder was effectively chronic mania, and that without clear episodes of major depression, "the validity of this diagnosis is called into question" (p. 847).

The significance of the roundtable is highlighted by its host: NIMH is the pre-eminent governing body for mental health research within the entirety of the US, and the acceptance of the PBD phenotypes at this level would have been extremely influential in furthering the national spread of what became an "epidemic of childhood bipolar disorder" (Frances 2010b). However, the NIMH roundtable did not explicitly use the terms 'narrow' and 'broad', at least in their published report in *JAACAP*. They did state:

> Investigators studying BP-I and BP-II phenotypes that fit *DSM-IV* criteria in prepubertal children noted that the most frequent course is a long-duration episode with rapid cycling (ultradian or continuous cycling as the predominant type) and mixed mania (i.e., co-occurring mania and depression) (e.g., Geller et al., 2000a, 2001a). (Notelmann et al. 2001, p. 871)

The 2005 '10-year review' also cited a 2003 article from Ellen Leibenluft (then Director of the Pediatric and Neuropsychiatry branch of the NIMH) and colleagues that sought to bring clarity to the definitions used for bipolar disorder in the paediatric age range. Leibenluft and colleagues (2003) suggested the term 'narrow' phenotype be used for children who met full DSM-IV criteria for bipolar disorder, including duration-of-episode criteria of 4 days (hypomania) and 7 days (mania). Further, they suggested two 'intermediate' phenotypes:

firstly, one comprising the 'ultradian' cycling and 'ultra-rapid' 1 – 3-day cycles described by the WUSL group, and secondly, another of demarcated 'irritable without elevation' mood episodes. Finally, Liebenluft et al. recommended the term 'broad' phenotype PBD be applied to the chronically irritable cohorts described by the MGH-Harvard group (Leibenluft et al. 2003).

This overview of Leibenluft et al. (2003) was an important article, appearing in the *American Journal of Psychiatry*. The article strove to provide much needed semantic clarity to a complex and confused terminology. It set the bar high and maintained consistency with DSM-IV for what could be diagnosed as Bipolar-I or Bipolar-II disorder in the paediatric age range. Leibenluft and colleagues implied the 'intermediate' phenotypes were really still research hypotheses, while the ground was set for moving chronic irritability away from the realm of bipolar disorder.

Unfortunately, the term 'intermediate' phenotype PBD was not to be taken up by researchers in the ensuing published literature: 'PBD' continued to be applied to all types of 'bipolar disorder' in the paediatric age range. 'Broad phenotype' PBD gradually became used for the chronically irritable group and other forms of PBD often were referred to as 'narrow phenotype' in contrast. While no formal PBD diagnosis was ratified in the forthcoming DSM-5, the sequestering of the 'broad phenotype' PBD construct eventually led to the creation and inclusion of the new diagnosis DMDD (Chapter 4.8.5). Despite this, the MGH-Harvard group continued to publish with the term PBD, without using the new DMDD classification, after the publication of DSM-5; for example, in an article titled: "Pediatric mania: the controversy between euphoria and irritability" (Serra et al. 2017) where Biederman and colleagues noted: "… the phenomenology of paediatric mania is still highly debated" (p. 386). They claimed:

> Irritability has been reported to be the most frequent clinical feature of pediatric mania reaching a sensitivity of 95–100% in several samples. Only half the studies reviewed reported on number of episodes or cycling patterns and the described course was mostly chronic and ultra-rapid whereas the classical episodic presentation was less common (p. 386).

This is a clear demonstration that some authors, at least in some publications, continue to refer to 'broad phenotype' PBD post-DSM-5.

3.3 **Preschool and infantile onset of PBD**

While the new definitions of states of so-called mania were primarily what distinguished the phenotypes, an equally controversial shift was the application of the hypothesised diagnoses to very young children. Both the WUSL and the MGH-Harvard research groups counted cases of not just pre-pubertal children, but also pre-schoolers and toddlers.

Specifically, the 'narrow phenotype' PBD was reported as being found in 26 (8.6%) of a community sample of three hundred and three 3 – 5-year-old preschool children, based on structured interviews of mothers, by WUSL researchers (Luby & Belden 2006). The mothers of the PBD children were more likely to be single with lower income and less education than mothers of the other three groups defined in the study (Healthy, Major Depressive Disorder (MDD) or Disruptive Behaviour Disorder (ADHD, ODD and CD) groups). The structured interview used was the Preschool Age Psychiatric Assessment (Egger, Ascher & Angold 1999) which omitted DSM-IV duration criteria for the PBD and MDD groups. The authors noted that not using DSM duration criteria was the main limitation of their study but justified this on the basis that the MDD and PBD groups were impaired by their emotional dysregulation. Further, the authors noted the issue of emotional dysregulation and fantasy being normative in preschool children, but assert that such fantasies are "signs of more serious underlying clinical symptoms":

> As stated, identifying clinically significant grandiose behavior in preschoolers is complicated by the fact that overestimating abilities, highly favorable self-impressions, and expressions of excessive self-confidence are viewed as normative features of this developmental period (Stipek, Feiler, Daniels & Milburn, 1995). … However, as evidenced in the current investigation when young children develop overly positive and elevated self-concept beliefs that are fixed, not reality based, and extend beyond these domains, they appear to be exhibiting signs of more serious underlying clinical symptoms and possible manifestations of grandiosity. Some clinical examples … preschoolers who believe, and act on the belief, that they can and should direct the household or preschool, give instructions to physicians and other authority figures that they expect to be followed, or who feel they have supernatural powers or abilities such as the ability to change the weather at will. (Luby & Belden 2006, p. 976)

Alternatively stated, the WUSL research group appeared to interpret the fixed fantasies of young children as evidence of delusional beliefs. As described above, other traditions in developmental psychology and child and adolescent mental health would interpret such fixed beliefs in terms of Piaget's concept of pre-operational thinking and psychodynamic defences against family and other systemic stressors.

In their own study, the MGH-Harvard group reported that 23% of preschool-age children referred to their outpatient clinic were diagnosed to have PBD based on structured clinical interviews. The mean age (SD) of the 44 pre-schoolers was 5.1 ($\pm$ 0.8) years-old; the mean age of onset of symptoms was 2.5 ($\pm$ 1.4) years-old and the mean number of 'lifetime manic episodes' was 7.7. The rate of comorbid DSM diagnoses was 100% with 95% ADHD, 41% CD, 91% ODD and 70% with anxiety disorder (Wilens et al., 2003). These were extraordinary statistics, when compared against the generally accepted levels of bipolar disorder in the overall population (Chapter 1.3). Further, it was the subsequent exploration of drug treatment options in children of this age that also crossed the boundaries of currently recommended practice standards.

3.3.1 **Medicating young children**

For half a century, the mainstay of pharmacotherapy for bipolar disorder, particularly the classical Bipolar-I disorder, has been lithium. Lithium has been shown to reduce recurrence and severity of both future manic and depressive episodes (Malhi, Adams & Berk 2009; Malhi, 2017). It is important to note though, that a systematic review of the drug trials evidence for lithium found the evidence for anti-manic and specific bipolar disorder prophylaxis to be weak and use has to be weighed against its significant toxicity (Moncrieff, 1997). Second to lithium in this regard have been several of the anticonvulsant class of medications, notably sodium valproate. Healy (2006) notes that the term 'mood stabilizer' had barely been used in the literature until 1995 when "Abbott Laboratories got a license for using the anticonvulsant sodium valproate (Depakote) for treating acute mania" (p. 0441): a veritable explosion of the use of the term 'mood stabilizer' followed.

Sedative medications like phenobarbital, benzodiazepines and the first-generation antipsychotics (FGAs) such as haloperidol and chlorpromazine had long been used to suppress acute manic symptoms. Then, from the late-1990s, pharmaceutical companies aimed to have

their newly on-patent atypical antipsychotics, such as olanzapine, quetiapine, risperidone, aripiprazole and ziprasidone, that were coming to market, designated as mood stabilizers for long-term maintenance treatment of a growing market of bipolar disorder sufferers. As Healy noted this included running "trials of Risperdal and Zyprexa on children with a mean age of four years old (Mick et al., 2004)" (Healy 2006, p. 0444).

As stated by the American Academy of Pediatrics, the US Food and Drug Administration (FDA) approves drugs when the manufacturer, through a process involving four phases of clinical trials, has proven the drug to be "safe and effective" for the "particular condition" as assessed by the FDA (AAP 2016). Despite the absence of FDA approval for the use of atypical antipsychotics in children under age 11 (exceptions being for irritability with behaviour disturbance in autistic children age 6 and older), as reproduced in Figure 3.1 below (CMS & Medicaid Integrity Group 2013), PBD researchers made the decision both to administer antipsychotic drugs to very young children, and commence research examining the impact.

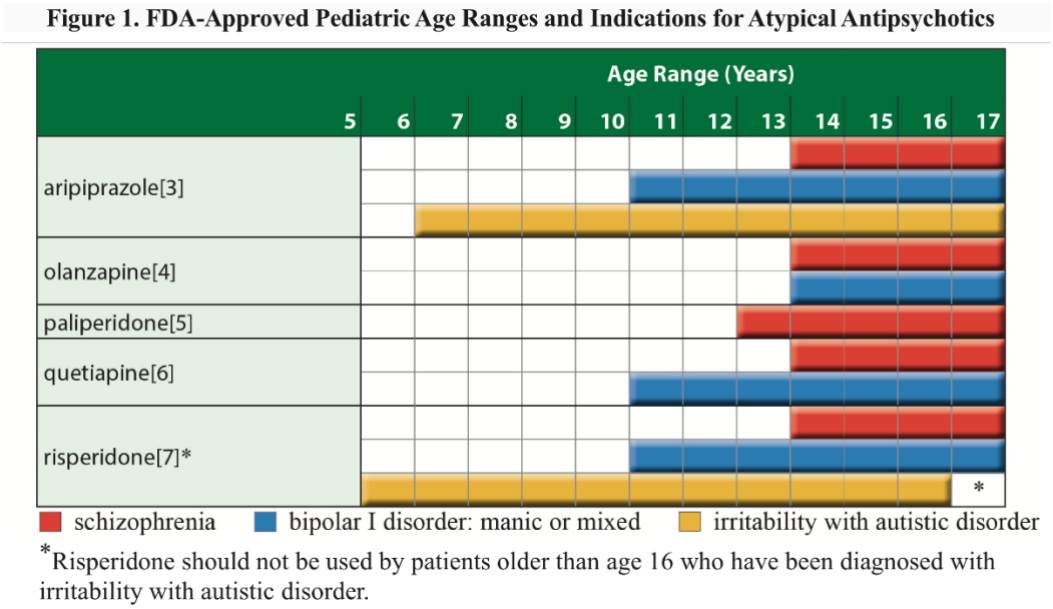

Figure 3.1: FDA- Approved Pediatric Age Ranges and Indications for atypical antipsychotics (CMS.gov factsheet, August, 2013, https://www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Pharmacy-Education-Materials/Downloads/atyp-antipsych-pediatric-factsheet.pdf)

For example, the MGH-Harvard group conducted a comparison of olanzapine versus risperidone in thirty-one 4 – 6-year-old children (Biederman, Mick, Hammerness, et al. 2005); an open-label trial of quetiapine (Joshi, Petty, et al., 2012); and a trial of olanzapine and topiramate (Wozniak et al. 2009) in the same age group.

The Biederman et al. (2005) study was an open label 8-week drug trial that claimed treatment with both olanzapine and risperidone "may result in a rapid reduction of symptoms of mania in preschool children." However, "because of substantial residual symptomatology and adverse effects" there was a "pressing need to identify safe and effective treatments" in this "high-risk" preschool "population" (p. 589). The article reported a marked rise in prolactin with both drugs, and children gained 10% and 15% of body weight on risperidone and olanzapine respectively. Prolactin is intricately involved in sexual development. To have raised prolactin through childhood, puberty and adolescence is concerning, and indeed gynaecomastia and infertility are two reported adverse effects (Holzer and Eap, 2006). Further, the FDA's level of significant "treatment emergent abnormal weight gain" in a clinical drug trial is a "7% increase from baseline" (Nihalani et al. 2011, p. 2).

Other drug trials in very young PBD cohorts include a "72-week maintenance study" of aripiprazole versus placebo for "96 outpatient children, 4 – 9-years-old" (Findling et al. 2012), cited in the recent ISBD Task Force on PBD report (Goldstein et al. 2017) as an example of first-line therapy. The medication aspect of the PBD phenomenon is discussed further: suffice to note here the controversy surrounding PBD escalated on the issue of giving psychotropics to preschool children.

3.4 Concluding comments

Overall the classical view has been that the first episode of mania or hypomania generally presented from late adolescence into adulthood, with rare peri-pubertal and early adolescent cases and pre-pubertal cases either exceptionally rare or non-existent. The debate as to whether the disorder even occurs in children or not has occasionally been revived since the 19th century and again rose in the US from the 1970s onwards with the reconceptualization that mania in children presented differently. By the mid-1990s two US academic child psychiatry centres had presented research on cohorts of pre-pubertal children, asserting two 'phenotypes' of hypothesised PBD. The PBD hypothesis was well accepted and highlighted by *JAACAP* and some other US based journals, and given further impetus, at least within the US, by the NIMH. Treatment of very young children with mood stabilisers such as sodium valproate, and atypical antipsychotics as purported mood stabilisers, and subsequent drug trials, ensued without formal ratification of the PBD hypotheses in either the current DSM or ICD versions.

CHAPTER 4. OVERVIEW OF THE US PBD 'EPIDEMIC'

4.1 Introduction

Having established the context into which the proposed PBD hypotheses emerged, this chapter provides an overview of the key literature and events, from both psychiatric and public sources, that contributed to the evolution of the PBD hypothesis and its subsequent decline. What follows is a complex story: a straightforward literature review could not contain the full narrative and extraordinary events that have marked the course and impact of the PBD hypothesis. Not only published articles but the journals themselves, debates at conferences, the role of the NIMH, CME, sponsoring pharmaceutical companies and professional psychiatric bodies needed to be considered. The tragedy of the death of a small child from the effects of psychotropic medication, a senatorial inquiry into undisclosed conflicts of interest on the part of some PBD researchers, and the role of the media in publicising these events also form part of the story.

The first half of the chapter therefore covers material mostly extraneous to the academic literature, whereas the second half comprises a critical literature review of the key articles, debates and themes in the academic literature and conferences.

In essence, PBD occurred during a time of dominance of the biomedical-reductionist, descriptive psychiatric paradigm particularly in US psychiatry. There was a focus on quantitative research rather than qualitative and reliance on symptom check-list questionnaires with widened parameters of DSM criteria for bipolar disorder. PBD as a diagnosis received widespread support from US psychiatry journals, conferences and CME, research was well-sponsored by the pharmaceutical industry as was also the advocacy group the Child and Adolescent Bipolar Foundation (CABF), which contributed to a burgeoning genre of self-help books for parents and story books for children about PBD. The media

provided favourable coverage as seen for instance in a 2002 TIME magazine article and highlighted on *The Oprah Winfrey Show*. Criticism and debate in US child psychiatry was muted.

Unsurprisingly, there was a rapid translation of the PBD hypothesis from research units to clinics, and the diagnosis spread widely within the US.

The rapid rise in clinical diagnoses and expansion of pro-PBD literature and conference presentations with minimal published academic debate slowed following the tragic death of 4-year-old Rebecca Riley in Massachusetts in December 2006. This drew a more critical media spotlight and allowed researchers and clinicians who adhered to the classical perspective of bipolar disorder as a rare mid-adolescent-onset disorder, to air opinions that had been missing from journals and conferences.

In 2008, the Senator Grassley inquiry into conflicts of interest between the pharmaceutical industry and the medical profession drew attention to some PBD researchers. The over-medicating of children became both a media and academic focus, as did the biomedical-reductionist paradigm and use of descriptive psychiatric criteria devoid of a child's lived experience. Allied to this was awareness of 'diagnostic upcoding' in the US health care system.

In recent years, international researchers contributed evidence to the early stages of developing bipolar disorder that at the time of submission of this thesis, suggest the classical perspective remains most accurate. Longitudinal high-risk offspring studies have confirmed late adolescent to adult onset of the first manic or hypomanic episodes, but less specific anxiety, sleep and minor depressive disorders precede diagnosable bipolar disorder by some years in those with high genetic risk. Debates over the community prevalence of bipolar disorder in children and youth are ongoing.

To assist the reader in following this history, two extensive timelines showing key articles, conference and media debates, and so forth, comprise Appendix B. The first timeline lists articles and events that favoured the PBD hypothesis, the second lists key articles and events that were sceptical of the PBD hypothesis and promoted the classical perspective.

At this point, a graph of the number of PBD articles, by year published, illustrates the rise and decline of the PBD hypothesis in the academic literature (Figure 4.1). Using the *Scopus* database, a specific body of PBD literature was identified on 23 January 2018; using the search terms ("paediatric bipolar" OR "pediatric bipolar" OR "juvenile bipolar" OR "childhood bipolar" OR "paediatric mania" OR "pediatric mania" OR "childhood mania" OR "juvenile mania"), 789 articles were found to the end of 2017.

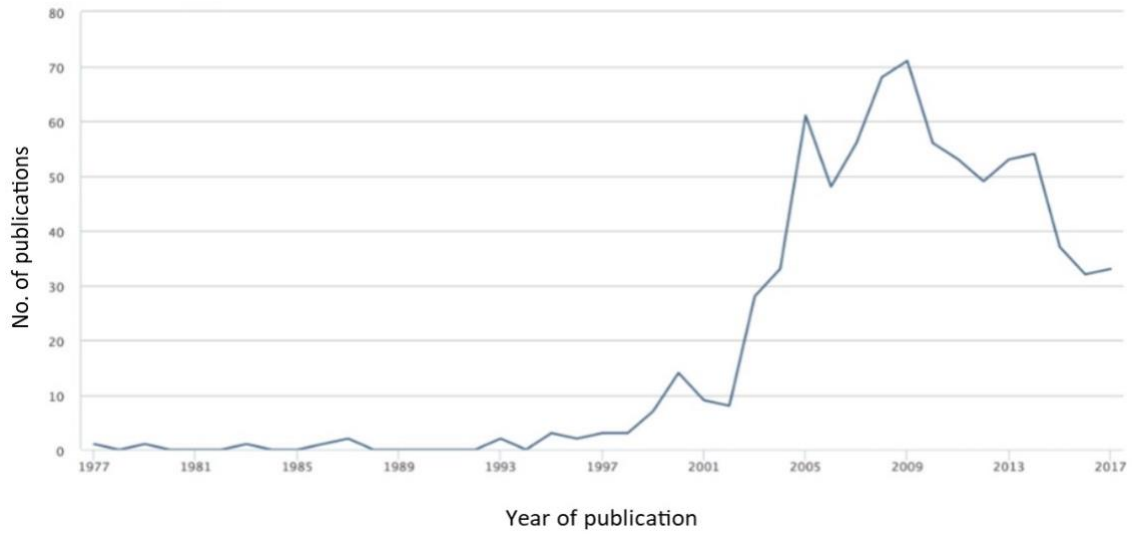

Figure 4.1: Number of PBD publications by year of publication (Source: personal collection)

While Figure 4.1 refers to the number of PBD articles published, a second figure fills out the story: in the US between 1994/5 and 2002/3 the diagnosis of bipolar disorder amongst children and teens rose 4,000% in US outpatient primary care clinics, albeit from a low base, but with a still steeply rising trajectory in 2003 (Moreno et al. 2007, p.1034; Figure 4.2).

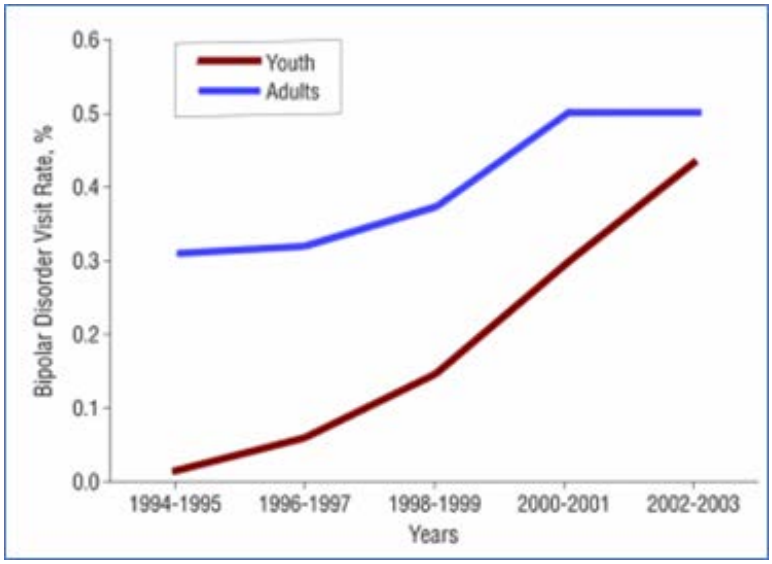

Figure 4.2: Bipolar disorder visits to US primary care clinics (Moreno et al, 2007, p. 1034). Reproduced with permission.

This large increase was described by Frances, chair of the DSM-IV task force, writing in the *Psychiatric Times*, the lead news journal for US psychiatrists, as an "epidemic of childhood bipolar disorder" (Frances 2010b).

4.2 Influence of the pharmaceutical industry

4.2.1 Overview of Pharma influence in the PDB epidemic

A major theme of the expansion of PBD from a research hypothesis to an overdiagnosis epidemic, was the influence of the pharmaceutical industry through sponsoring of research, CME, the advocacy group the Child and Adolescent Bipolar Foundation (CABF), and the wider direct-to-consumer advertising of 'mood stabilisers' and bipolar disorder as an allegedly common diagnosis via the mass media.

There is an extensive literature on industry influence on researchers via grants and sponsored studies, payment for being on speakers' bureaus and guidelines committees as KOLs (Perlis et al. 2005; McHenry & Jureidini, 2009), and on journals via dependence on advertising and reprint revenue has been well critiqued in the literature (Smith, 2005; Lexchin & Light, 2006; Lundh et al. 2010) and further exploration of this will occur in this literature review. By way of example, a 2005 'treatment guidelines' review for PBD published in *JAACAP* (Kowatch et al. 2005) were sponsored by seven pharmaceutical companies and focused almost solely on pharmacotherapy.

4.2.2 **Conflicts of interest between psychiatry and the pharmaceutical industry**

Concerns about Medicine-Pharma conflicts of interest had been growing since the start of the 21st century. Chief Editors of prestigious medical journals made what once would have been astounding claims: Richard Horton, chief-editor of *The Lancet,* titled an editorial "Just how tainted has medicine become?" and answered in the text: "heavily, and damagingly so, is the answer" (*The Lancet*, 2002). Richard Smith, a long serving chief-editor of the *British Medical Journal,* penned an article titled: "Medical journals are an extension of the marketing arm of pharmaceutical companies" upon his retirement from the *BMJ* (Smith, R 2005). Marcia Angell, chief-editor of *The New England Journal of Medicine*, published an academic article titled: "Industry-sponsored clinical research: a broken system" (Angell 2008) and a public media article: "Drug companies and doctors: a story of corruption" (Angell 2009). She found that psychiatry, with the ubiquitous nature of stress, anxiety and unhappiness in modern societies, holds large markets for tranquilizers, anxiolytics and drugs called antidepressants. Angell indicated that this large and elastic market was ripe for commercial exploitation.

As defined in a 2002 article, "disease-mongering" was coined to describe "medicalising ordinary life" in order to widen "the boundaries of treatable illness in order to expand markets for those who sell and deliver treatments" (Moynihan, Heath & Henry 2002, p. 886). The term was widely adopted: Moynihan's article has 1,279 citations in Google Scholar (as of 27 March 2019). In their article on PBD as an example of disease-mongering, Healy and LeNoury (2007) point out:

> Studies run by academics that apparently display some benefits for a compound have possibly become even more attractive to pharmaceutical companies than submitting the data to the FDA in order to seek a license for the treatment of children. Companies can rely on clinicians to follow a lead given by academics speaking on meeting platforms or in published articles. The first satellite symposium on juvenile bipolar disorder at a major mainstream meeting, the American Psychiatric Association meeting in 2003 featured the distinguished clinical faculty of MGH. The symposium was supported by an unrestricted educational grant. … The power of companies does not lie in dictating what a

> speaker will say but in providing platforms for particular views … As an additional benefit, academics come a lot cheaper than putting a sales force in the field. (p. 218)

An opinion piece in *The Lancet* noted the dramatic paradigm shift in psychiatry from the mid to late 20th century, from a time when psychoanalysis dominated to a current era where a "simplistic biological reductionism rule[s] the psychiatric roost" (Scull 2010). Scull attributed this to conflict of interest factors:

> [D]rug money has come to dominate psychiatry. It underwrites psychiatric journals and psychiatric conferences (where the omnipresence of pharmaceutical loot startles the naive outsider). It makes psychiatric careers, and many of those whose careers it fosters become shills for their paymasters, zealously promoting lucrative off-label uses for drugs ...
>
> And it controls psychiatric knowledge in multiple ways … The very categories within which we think … are manipulated and transformed to match the requirements of the psychiatric marketplace … (p. 1247)

Scull noted that: "patients and their families learned to attribute mental illness to faulty brain biochemistry" (p. 1247). It is in such an atmosphere that normal range reactions to stress past, present and anticipated can be given status as signs of underlying biochemical disease states. This then leads to the unnecessary prescribing of psychotropic medication in the first place, and the concept that long-term medication is needed, where short term symptom amelioration may have sufficed.

Psychiatric nosology itself has been noted to be subject to pharmaceutical industry influence. DSM committees are a key place for the widening of disease boundaries. Financial conflicts of interest between the industry and members of the DSM-IV and DSM-5 panels have been significant. Of the 170 DSM-IV panel members, 56% had one or more financial associations with pharmaceutical companies, and it was 100% of members of the Mood Disorders panel as well as for the Schizophrenia and Psychoses panels (Cosgrove et al., 2006). The authors make note that "in light of the extreme profitability of the psychotropic drug market – particularly for antidepressants and atypical antipsychotics – that 100% of members of those

panels having financial ties to the pharmaceutical industry were a "cause for concern" (Cosgrove et al., 2006).

In the face of increasing criticism of the APA for such conflicts of interest, the APA's stated goal was for the DSM-5 committees to be "free from any conflicts of interest", however 67% of the Mood Disorders panel still registered financial ties to industry (Cosgrove & Krimsky, 2012). The loosening of criteria for bipolar disorder in sequential editions of the DSM need be seen in this light.

As mentioned, Frances, the chair of the DSM-IV committee, who had described PBD as a "false diagnostic epidemic" (Frances 2010b; Chapter 3.2.3) also laid much of the blame for the epidemic on conflicts of interest between researchers and industry (also Ch. 4.8.2.24).

4.2.3 **Bipolar disorder and PBD in internal industry documents**

Taking this further, Levin and I argued that conflict of interest between academic researchers and pharmaceutical companies was a likely contributor to the PBD hypothesis (Levin & Parry 2011; Appendix A15). Our article was by invitation from the editor of *Adolescent Psychiatry*. The data Levin and I referred to for our hypothesis came mainly from internal industry documents released in litigation by US federal and state prosecutors against the pharmaceutical industry primarily for off-label marketing violations. These industry documents were released or leaked to the public and posted online. Psychotropic medications and in particular on-patent atypical antipsychotics featured prominently in the litigation and documents.

Glen Spielmans (Metro State University, Minnesota) and I reported on themes emerging from an examination of over 400 documents involving mainly atypical antipsychotics and some antidepressants (Spielmans & Parry 2010) (Appendices A10 & A11). It seemed that conflict of interest problems were widespread in the way information was being presented to physicians in the academic literature and in CME. We titled our article "From evidence-based medicine to marketing-based medicine: evidence from internal industry documents".

Internal pharmaceutical company documents were posted on several websites. Many are housed on the *Drug Industry Document Archive* set up at the library of the University of California, San Francisco (see URL: http://dida.library.ucsf.edu/). A larger analysis of these

and other documents that were researched for my article with Spielmans exists at URL: http://www.healthyskepticism.org/global/news/int/hsin2009-12 .

The documents we read mainly concerned the antipsychotics olanzapine (Zyprexa) by Eli Lilly, quetiapine (Seroquel) by AstraZeneca and risperidone (Risperdal) by Janssen. The companies saw expansion of the diagnostic boundaries for bipolar disorder as a way to increase sales of these on-patent atypical antipsychotics in the early 2000s when patents for the blockbuster selling SSRI antidepressants were starting to expire (the industry uses the term 'blockbuster' for any drug with annual sales above US$1 billion). The documents implied that efforts could be made to rebadge these medications as 'mood stabilizers' for prophylactic use in bipolar disorder: as this thesis has demonstrated, these efforts were at least partly successful.

4.2.4 **The slim case for aripiprazole as a 'mood stabilizer'**

An example of rebranding an atypical antipsychotic as a mood stabilizer is aripiprazole, manufactured by Bristol-Myers Squibb (BMS) under brand name Abilify. Aripiprazole received FDA approval for maintenance treatment of bipolar disorder in 2005. This provided a bonanza for BMS as total sales of aripiprazole increased from US$1.5 billion to US$4 billion between 2005 and 2009 (IMS Health 2010). There was an apparent wealth of research supporting this indication. However, a systematic review of the literature for aripiprazole as maintenance therapy for bipolar disorder published in *PLoS Medicine* (Tsai et al. 2011; Appendix A16) found that this apparently large evidence base rested upon a single multicentre study by Keck and colleagues (Keck et al. 2006; Keck et al. 2007).

The Keck et al. study initially enrolled 633 subjects with acute mania. It had a 6 – 18-week stabilization phase, a 26-week double-blind placebo-controlled phase and a 74-week extension phase at end of which only five subjects in the placebo arm and seven in the extension arm had not relapsed. The conclusion from Keck and colleagues was:

> Over a 100-week treatment period, aripiprazole monotherapy was effective for relapse prevention in patients who were initially stabilized on safety and tolerability profile. (Keck et al. 2007, p.1480)

We argued there were four problems with the study:

1. insufficient duration to demonstrate maintenance efficacy;

2. limited generalizability due to enriched sample of aripiprazole responders in acute manic episode;
3. possible conflation of iatrogenic adverse effects of abrupt medication discontinuation with beneficial effects of treatment; and
4. low overall completion rate. (Tsai et al. 2011, p. 1).

There were just 12 subjects from an initially enrolled 633 who completed the full maintenance extension phase. We identified 80 citations to the two Keck et al. articles including eight major review articles and three treatment guideline documents. Seventy-six of the 80 citing articles and all 11 major reviews and treatment guidelines positively reported aripiprazole as effective for maintenance therapy of bipolar disorder without any mention of study limitations. Ten of the 11 reviews and guidelines articles carried author disclosure statements for BMS. Influential articles and treatment guidelines were all based on a single flawed study with a very small completion rate.

4.2.5 **Editorial and lead article in *ANZJP* emphasise lithium over antipsychotics**

In contrast, and as a response to this general trend in the literature, the *ANZJP* ran a lead article (Malhi, Adams & Berk 2009) and editorial (Malhi & Gershon 2009) in the December 2009 issue. In a letter to the journal (Parry 2010a; Appendix A13) I referred to these articles, commenting that:

> The editorial [1] and lead paper [2] in the December 2009 issue of this Journal both rightly champion lithium as an effective mood stabilizer; indeed, perhaps the only agent truly warranting that term based on level 1 (systematic review of all clinical trials) evidence. However, both articles note lithium lacks a 'commercial champion' [2] and is under-prescribed as 'agents that had stronger commercial backing soon eclipsed it' … even though lithium has 'endured competition' from antidepressants and anticonvulsants it is currently 'the atypical antipsychotics that form the charge, with their eager migration into the lucrative mood stabilizer arena' [1].

> … Internal industry documents do indeed confirm the eagerness with which some companies are trying to position their atypical antipsychotics in the 'lucrative mood stabilizer arena'. (p. 585)

4.2.6 **Eli Lilly sought 'mood stabilizer' tag and more bipolar diagnoses**

As we outlined in our examination of industry documents (Spielmans & Parry, 2010):

> Eli Lilly's original "lifeplan" document for olanzapine in 1994 described the marketing profile for olanzapine as the "safer clozapine"; the market was to be schizophrenia and there was no mention of bipolar disorder (Eli Lilly 1994). However, the company's patent on its bestselling antidepressant fluoxetine (Prozac) was due to expire in August 2001. Slides from a PowerPoint presentation at a meeting of the "Zyprexa Product Team", 25 July 2001, stated "The company is betting the farm on Zyprexa. The ability of Eli Lilly to remain independent and emerge as the fastest growing pharma company of the decade depends solely on our ability to achieve *world class commercialization of Zyprexa*" (Eli Lilly 2001c, italics in original). (p. 25) (Figure 4.3: Zyprexa Product Team Off-site July 25, 2001, ZY201548768 (Eli-Lilly & Company 2001, p. 4)).

Figure 4.3: Zyprexa Product Team Off-site July 25, 2001, ZY201548768 (Eli-Lilly & Company 2001, p. 4)

> Graphs and text in the "Zyprexa Product Team summary" from 1997 referring to "Global Zyprexa Bipolar Forecast" indicated sales projections for the year 2000

would increase more than fourfold if Zyprexa could be viewed as a “Depakote-like ... MOOD-STABILIZER” rather than a “Risperdal-like ... Antipsychotic” (Tollefson 1997). (p. 25) (Figure 4.4: Zyprexa Product Team – 4 Column Summary, ZY200270343, (Eli Lilly & Tollefson 1997, p. 41))

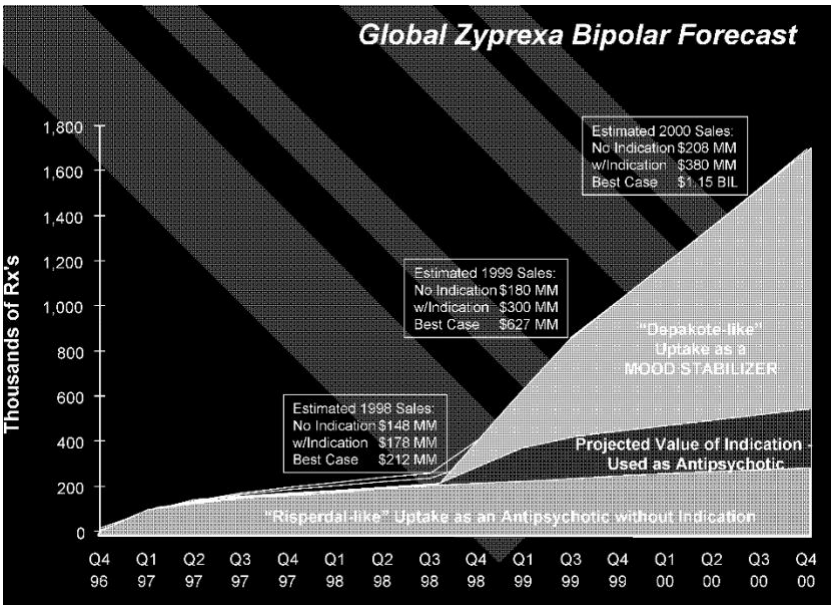

Figure 4.4: Zyprexa Product Team – 4 Column Summary, ZY200270343, (Eli Lilly & Tollefson 1997, p. 41)

A slide titled “Bipolar Vision of Product Evolution” stated: To be a leader in the bipolar market, Zyprexa will need to be viewed as a *true mood stabilizer* (Eli Lilly 1997b) (p. 25) (Figure 4.5: Zyprexa Product Team – 4 Column Summary, ZY200270343, (Eli Lilly and Tollefson, 1997, p. 49) (Figure 4.5).

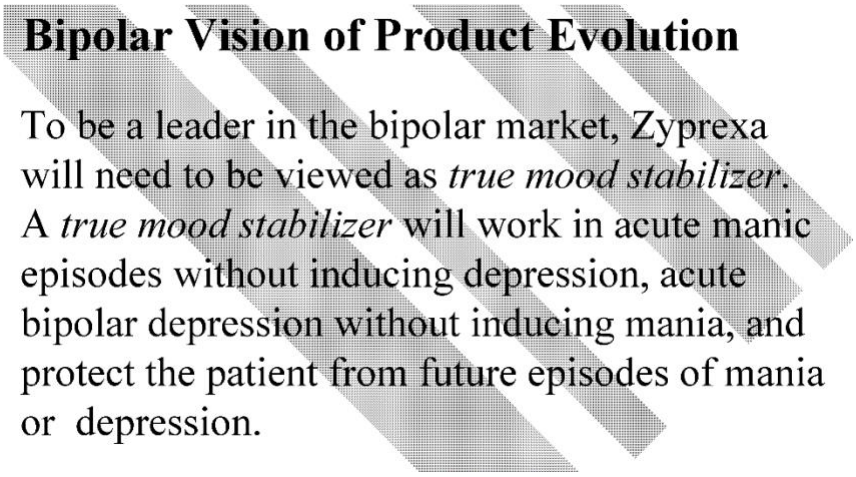

Figure 4.5: Zyprexa Product Team – 4 Column Summary, ZY200270343, (Eli Lilly and Tollefson, 1997, p. 49)

These are noble aims, but the same internal company presentation included a SWOT analysis indicating under "weaknesses" that the company did not yet have the data to support such a goal (Eli Lilly, 1997c). (p. 25) (Figure 4.6)

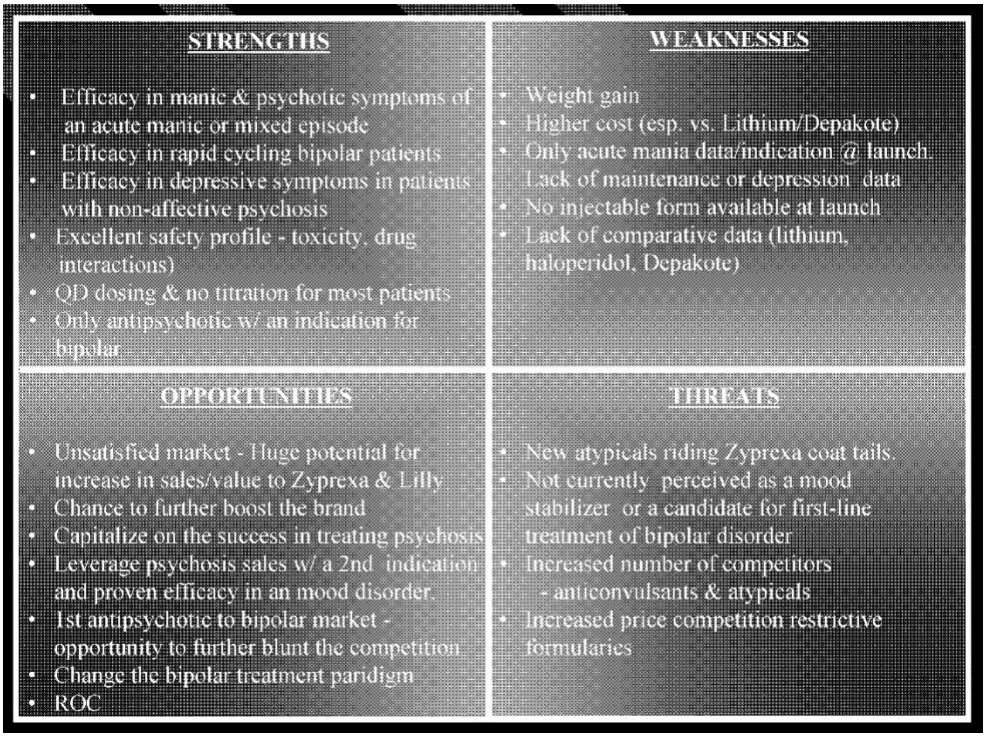

Figure 4.6: Zyprexa Product Team – 4 Column Summary, ZY200270343, (Eli Lilly & Tollefson 1997, p. 50)

An internal company PowerPoint presentation on “Zyprexa PCP [Primary Care Physician] Vision” stated that a goal was to “Expand our market by redefining how primary care physicians identify, diagnose and treat complicated mood disorders (i.e. Bipolar Disorder)” (Eli Lilly 2001b). (p. 25) (Figure 4.7)

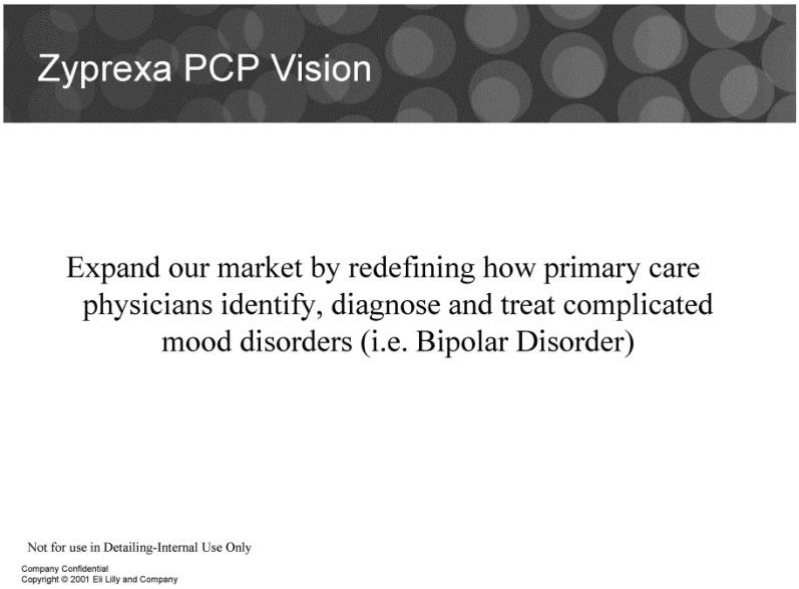

Figure 4.7: Managed Care - June 2002 Information about Zyprexa (olanzapine), ZY200083405, (Eli-Lilly 2002, p. 2)

It was not so easy to convince primary care physicians to diagnose bipolar disorder as a relatively common disorder. Another slide (Figure 4.8):

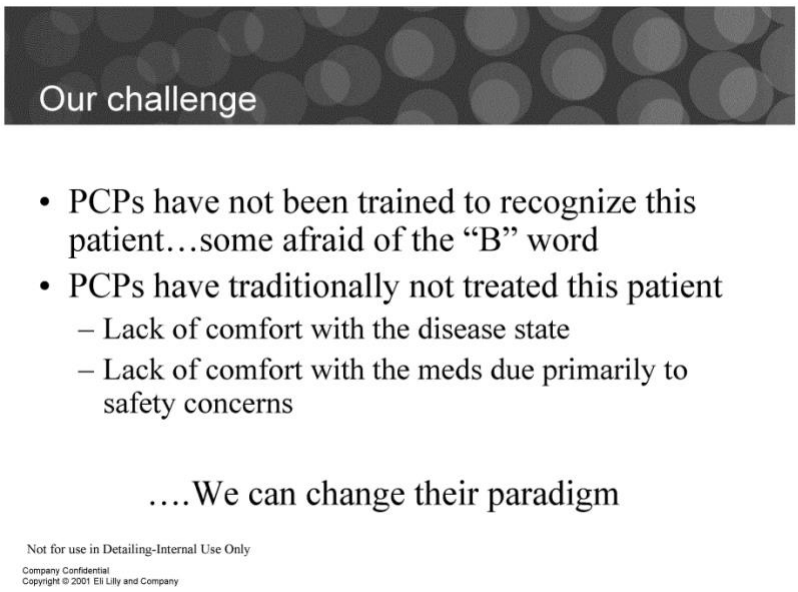

Figure 4.8: Managed Care - June 2002 Information about Zyprexa (olanzapine), ZY200083405, (Eli-Lilly 2002, p. 4)

> [S]hows that the move into primary care was recognized as a challenge. Physicians in primary care did not typically treat bipolar disorder and used antipsychotic medications infrequently, partially due to safety concerns. The company, however, aimed to "change their paradigm". Part of this marketing campaign was to broaden the concept of bipolar disorder to include "complicated mood," comprising some combination of anxiety, disruptive sleep, irritability, and mood swings (Spielmans, 2009). (p. 25)

Of particular note, the Eli Lilly slides included "Juvenile Mania" in the timeline to "generate the bipolar data needed" for a rollout of regulatory indications for Zyprexa in the treatment of bipolar disorder (Figure 4.9).

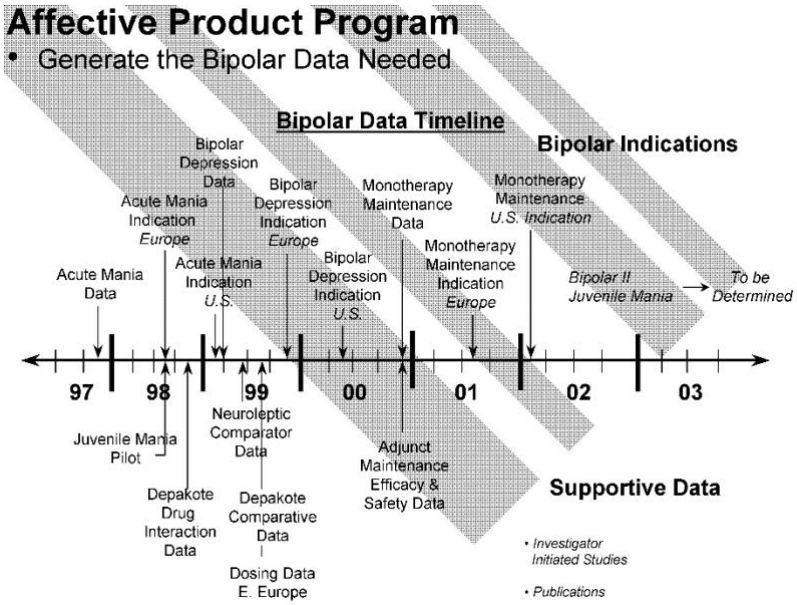

Figure 4.9: Zyprexa Product Team – 4 Column Summary, ZY200270343, (Eli Lilly & Tollefson 1997, p. 57)

Further indication of the company focussing on PBD was found in an email from a senior executive (later the CEO) of Eli Lilly, to other Eli Lilly executives. This email was reported in *The New York Times* from non-public company documents viewed in litigation in Alaska (Berenson 2008):

> "The fact we are now talking to child psychs and peds and others about Strattera means that we must seize the opportunity to expand our work with Zyprexa in this same child-adolescent population." (para. 6)

This email illustrates how pharmaceutical companies sought close relationships with prominent academic researchers, what are termed in the industry "Key Opinion Leaders" (KOLs).

4.2.7 **Janssen desire paediatric bipolar market for risperidone**

The media picked up the story. *The New York Times*, *The Wall Street Journal* and other media reported further revelations from internal industry documents, particularly from Janssen Pharmaceuticals Inc. involving the MGH-Harvard PBD researchers. The documents were released in the case of *Alma Avila, as next friend of Amber N. Avila vs Johnson & Johnson Company et al.* in the Massachusetts superior court, civil case number SUCV 2008-04392-A.

Alma Avila's daughter Amber had been treated with risperidone and other antipsychotics and the allegations were that benefits were overstated and side-effects understated. The documents are available at the following URL: http://psychrights.org/Research/Digest/NLPs/Risperdal/081112Opp2BiedermanQuash-Seal.pdf (Russell & LaMacchia 2008). The documents also feature in a 15-chapter online multi-media investigative series by the *Huffington Post,* (Brill 2015) available from: http://highline.huffingtonpost.com/miracleindustry/americas-most-admired-lawbreaker/ . Some documents are also housed in the *Risperdal litigation documents* section at the *drug industry documents archive* at the University of California, San Francisco available from: https://www.industrydocuments.ucsf.edu/docs/ (Wolfe 1999; Unknown 2002).

The value pharmaceutical companies place on partnering with KOLs was summarised by lawyers for the plaintiffs in "Appendix 1" of the court documents (see Appendix D2):

> March 2002 internal e-mail … by Gahan Pandina, the Assistant Director of CNS Clinical Development at Janssen Pharmaceuticals Products, L.P., regarding Dr. Biederman's presentation at an educational seminar involving over 1000 physicians, $700 CME course a week after Dr. Biederman had visited Janssen. The e-mail describes Dr. Biederman's presentation as being "very well-received" and that "the validity of the diagnosis of pediatric mania was completely accepted. [24] The e-mail also describes Dr. Biederman as not being "perceived to be aligned with any company in particular. [25] Also indicates that a topic of Dr. Biederman's presentation was that olanzapine (Zyprexa) should not be prescribed to children and adolescents due to its effect on metabolic issues. Describes Dr. Biederman's presentation as "a clear example of the utility of partnering with a group such as MGH [Massachusetts General Hospital], who has the potential of reaching and having a significant impact upon the field of child and adolescent psychiatry with these kind of professional activities in non-sponsored venues. [26]

This illustrated the value of KOLs to pharmaceutical companies, allowing for drug promotion outside the FDA regulatory pathways. This role of KOLs has been analysed further (Healy 2007). Anxiety within pharmaceutical companies over the risk of losing a KOL's collaboration to a competitor company is illustrated by further company documents in Appendix 1 of the court documents (see Appendix D3):

> November 1999 non-confidential e-mail chain [l5] in which John Bruins of Janssen "beg[s]" his supervisors to approve of a $3000 honorarium check for Dr. Biederman related to this physician's participation in a program at the University of Connecticut. The email states that … Dr. Biederman … is a very powerful national figure in child psych and … [since] a 280k proposal had been turned down [by Janssen] … "our business became non existant (sic) within his area of control. He now has enough projects with Lilly to keep his entire group busy for years.

In other words, the alleged tardy response by Janssen to a KOL's request for payment might have inadvertently fulfilled the wishes expressed in the internal Eli Lilly email reported by *The New York Times,* of being able to expand use of olanzapine in the paediatric market.

As *The New York Times* reported (Harris, G 2008b), the benefits flowed both ways. The "Janssen-Risperdal-MGH" documents showed that Biederman's group approached Janssen to set up a centre for researching PBD. Quoting from an email referenced in the court documents as JJRE02256029 and financial documents in Appendix 13 of the court documents:

> A February 2002 e-mail message from Georges Gharabawi, a Johnson & Johnson executive, said Dr. Biederman approached the company "multiple times to propose the creation" of the center. "The rationale of this center," the message stated, "is to generate and disseminate data supporting the use of risperidone in … [children and adolescents]." (para. 20)

However, the documents in Appendix 7 were summarised by the lawyers as showing that funding didn't come without company scrutiny of research outcomes:

> July 2, 2002, non-confidential e-mail chain initiated by Carrie Steffe … Total payments for this study were to be $369,000. [30] States to Dr. Biederman that the purpose of asking for information was that "Janssen Pharmaceutical is ... evaluating all ongoing research studies to ensure projects continue to align with our Business Strategy and that monetary and manpower (sic) resources are being efficiently allocated.

According to the 2002 annual report of The Johnson & Johnson Center for Pediatric Psychopathology at MGH (Appendix 14 of court documents) the mission plan for the centre (see Appendix D4) included three main goals:

> An essential feature of the Center is its ability to conduct research satisfying three criteria: a) it will lead to findings that improve the psychiatric care of children; b) it will meet high levels of scientific quality and c) it will move forward the commercial goals of J&J.

Goals to improve the psychiatric care of children and perform research of high scientific quality are admirably ethical. But to have as an equal goal to increase the sales of Risperdal can constitute a conflict of interest.

Also queried in the court documents and raised by *The New York Times* (Harris, G 2008b) and *The Wall Street Journal* (Amstrong & Mundy, 2008) was whether Professor Biederman had signed off on an altered data conference abstract at the request of a Janssen employee. The data was for a poster presentation at the 2002 annual meeting of AACAP. The study abstract, at least in an earlier draft, had according to Dr Pandina from Janssen shown a similar improvement on some outcomes for placebo as for risperidone. The abstract (Appendix D5) was approved by Biederman, who replied: "I will review this morning. I will happily sign the forms if you could kindly send them to me." The poster with the abstract was presented at the 2002 AACAP meeting and concluded that "Risperidone is effective in the treatment of manic and depressive symptoms frequently found in children with DBD. Implications for treatment are discussed." There was no mention of placebo having performed as well as risperidone; in fact, the opposite was stressed. The same abstract was presented at the 2003 annual meeting of the Society of Biological Psychiatry and eventually published (Biederman et al. 2006).

4.2.8 **Use of old Janssen data**

An interesting aspect of this study is that it was not of PBD *per se*, but a reworking of data from a previous Janssen sponsored study in Ohio (Aman et al. 2002) that had made *no* mention of mania, depression, bipolar disorder or PBD. The 118 children (97 of them males) had learning and disruptive behaviour disorders. The original study by Aman et al. recorded that it was "Supported by the Janssen Research Foundation." One retired psychiatrist, Dr J Mickey Nardo, blogging under the *nom de plume* of "1boringoldman", noted this fact and that the Biederman et al. article of 2006 in *Clinical Therapeutics* recorded its copyright under *Excerpta Medica*, a publishing firm neighbouring Janssen headquarters in New Jersey, which

has been allegedly implicated in ghost-writing scandals with Janssen (see http://1boringoldman.com/index.php/2011/07/03/bipolar-kids-postscript-detestable/ ; Nardo 2011). He also noted that the study had been concluded in 1998 (before PBD had gained much traction) according to http://clinicaltrials.gov/ct2/show/NCT00266552 .

Whereas the 2006 *Clinical Therapeutics* article clarified the retrospective reworking of Aman et al.'s data, a quick read of the poster abstract at the 2002 AACAP conference could have led attendees to conclude this was the MGH-Harvard group trialling risperidone for PBD.

4.2.9 **AstraZeneca's sponsoring of PBD research and CME**

Documents from the pharmaceutical company AstraZeneca included particularly damning evidence of serious conflicts of interest concerning KOLs. An email from the global marketing manager for Seroquel, AstraZeneca's atypical antipsychotic quetiapine, advised the suppression of negative data and rewarding of KOLs for compliance (Appendix D6). Professor Melissa Delbello was mentioned in AstraZeneca industry documents involving quetiapine for PBD in children (http://s3.documentcloud.org/documents/11067/astrazeneca-suit.txt, Case 2:04-cv--03479-BMS Document 46 Filed 04/27/10, pp. 11-12; US et al., 2008):

> 48. Dr. Melissa DelBello has been retained by AstraZeneca to help in its promotion of Seroquel to pediatric patients. In calendar year 2003, Dr. DelBello was paid $134,000 by AstraZeneca to assist in the marketing of Seroquel to pediatric patients. As of March, 2004, she has been paid $32,000 for 16 programs.
>
> 49. Dr. DelBello's single study concerns the use of Seroquel in combination with depakote for the treatment of mania in bipolar adolescent children. Dr. DelBello's study was funded by AstraZeneca. The scientific value of the study is questionable for the following reasons: 1) the sample on which the study is based includes only 30 patients; 2) the response rate is much higher than that of a larger study of 191 patients. Dr. DelBello's study claims an 87% response rate versus 53% in an FDA approved adult study.
>
> 50. Despite Dr. DelBello's purported findings, the AstraZeneca package insert for Seroquel reads: Pediatric Use - "The safety and effectiveness of Seroquel in pediatric patients have not been established."

> 53. In addition to paying Dr. DelBello directly, AstraZeneca supports her in other ways. AstraZeneca sales representative's "call notes" states that Dr. DelBello is very pleased that AstraZeneca is using her husband's catering business to do the off-label Seroquel lunches.
>
> 56. Dr. DelBello makes presentations throughout the United States. A presentation made in Pittsburgh, Pennsylvania, was with AstraZeneca's assistance linked to 30 separate satellite locations.

The Seroquel study mentioned in the prosecution deposition was published in *JAACAP* (DelBello, Schwiers, et al. 2002) and later cited in the therapeutic guidelines article (Kowatch et al. 2005) as the rationale for quetiapine's prominence in pharmacotherapy algorithms for PBD. Industry documents had shown AstraZeneca had suppressed data from several studies that showed poor antipsychotic response to quetiapine/Seroquel (Spielmans & Parry 2010). Therefore, as the prosecution deposition noted, in comparing this research with a similar NIMH sponsored study in adults, it is surprising that quetiapine would have performed well for acutely manic adolescents.

4.2.10 **Conclusions drawn from internal industry documents**

An inference drawn from the documents is that pharmaceutical companies are commercial enterprises. They have a fiduciary ethical responsibility to their shareholders. Unfortunately, this responsibility can be at odds with scientific and medical ethics. Like any capitalist enterprise, the creation of markets and exploiting of those markets through effective advertising are key methods to increase sales. A review of off-label marketing practices, based on whistleblower complaints that included the US et al. (2008) court documents listed above, concluded the practices were so widespread that no regulatory authority could contain them. Only increasing clinician awareness and vigilance of such practices by "physicians themselves [could] serve as a bulwark against off-label promotion" (Kesselheim, Mello & Studdert 2011, p. 7).

Therefore, the evidence suggests that industry approaches medical CME events with sophisticated marketing strategies. The fostering of KOLs within their specialities is seen as a powerful investment strategy. The academic literature is approached strategically, so that favourable data is highlighted and unfavourable data is not (Spielmans & Parry 2010).

A further implication is that the need for a larger market for on-patent atypical antipsychotics coincided with the looming loss of patents for SSRI drugs. This necessitated a shift from a paradigm of widespread depressive illnesses to a widened bipolar spectrum disorders concept. This included support for academics who theorised about "juvenile bipolar disorder" or "pediatric mania" (Figure 4.9; Appendix D3).

4.3 **Influence of advocacy groups, self-help books and advertising**

Among the key factors that drove expansion of awareness and diagnosis of PBD within the US were a best-selling book, a large well-funded advocacy organisation, and a genre of self-help books for parents of alleged 'bipolar kids' as well as story books on PBD for the children themselves. Additionally, websites and posters promoted the diagnosis as a previously unrecognised but common disorder afflicting pre-schoolers as well as older children and teens.

4.3.1 **Best-selling book: *The Bipolar Child***

In 2002, *The Bipolar Child: The Definitive and Reassuring Guide to Childhood's Most Misunderstood Disorder* was published. Written by Professor Demitri Papolos, an adult psychiatrist sub-specialising in genetics, and his wife Janice Papolos, the book sold several hundred thousand copies and was positively reviewed in *JAMA* by child psychiatry professor, Kiki Chang (Stanford University) for the third edition in 2007, where he noted that the book:

> [W]as at the forefront of an explosion of professional and public interest in pediatric bipolar disorder … instrumental in conveying the possiblitiy to thousands of parents that their child might have bipolar disorder – many made their way to our clinic, literally clutching a copy of the book. (Chang & Shah, 2007; p. 96)

Chang described: "Chapter 5, 'Prescriptions for Treatment'" as providing "detail regarding medications commonly used" and it was clear that serious mood stabilising cocktails were considered as Chang admonished the authors for "inaccurately" stating "that lamotrigine and carbamazepine should not be taken together with divalproex" as "untrue" (p. 96).

4.3.2 **The Juvenile Bipolar Research Foundation and online questionnaire**

Demitri Papolos, an adult psychiatrist with expertise in genetics, and his wife Janice Papolos, a medical media professional, had previously set up the JBRF which provided online parent education and a diagnostic questionnaire. He and his wife wrote *The Bipolar Child* and were closely associated with the CABF. In 2006 Papolos and colleagues, including Youngstrom (University of North Carolina), published a validation study of the JBRF online screening questionnaire, the Child Bipolar Questionnaire (CBQ) in the *Journal of Affective Disorders* (Papolos et al. 2006).

The diagnostic questionnaire could be self-administered by parents and older children and adolescents. A typical question from one of the JBRF questionnaires, the Jeffrey/ Jeanne Interview (JBRF 2005, p. 37) is illustrated in Figure 4.10.

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Figure Description: Question for "Jeannie", peripubertal girl, how often does she "feel silly and giddy and do funny things?

Access the Jeffrey/Jeannie Interview for Children via http://www.jbrf.org/the-jeannie-jeffrey-illustrated-interview-for-children/#

Figure 4.10: Question 3 from the Jeffrey/Jeanne Interview for Children (JBRF 2005, p. 37)

Janice Papolos also produced DVDs for parents such as *24: A day in the life of bipolar children and their families* and *Educating and Nurturing the Bipolar Child*. These were available via the website www.bipolarchild.com as was the screening questionnaire accessed via a tab titled

"Does your child have bipolar disorder? Complete and download a helpful screening inventory." The updated website (see http://www.jbrf.org/the-child-bipolar-questionnaire-for-families-use/, last accessed 2 March 2018) still has the questionnaire although one now needs to create a CBQ account first.

The 65-item CBQ was calibrated against the K-SADS-PL (Kiddie - Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version; Kaufman et al., 1997) and Papolos et al. found the "Core Index subscale" demonstrated "100% sensitivity and 86% specificity in classifying … [PBD]" (p. 149). The CBQ "takes approximately 10 min to complete and lends itself easily to self-administration via the internet or to administration by a clinician" (p. 156). In addition to the PBD phenotypes already in use, Papolos et al. listed a 'Core' phenotype of "elated and/or irritable" with "no duration required" but "overall disturbance must continue for at least 12 months" (p. 150). In other words, the "Core Index" with 100% sensitivity claimed to identify symptoms of mania *without* discrete episodes.

4.3.3 **The Child and Adolescent Bipolar Foundation (CABF)**

The CABF was set up as a self-help consumer organisation by "several hundred families" and included leading PBD researchers on their advisory board (*Medscape* 2000, para. 11). Primarily for parents of children diagnosed with PBD, different online links vary somewhat regarding the origins of the organisation and its programs; however, according to the popular online CME medical news media, *Medscape*:

> [T]he Child & Adolescent Bipolar Foundation (CABF) [was] a newly-founded national, not-for-profit organization of families raising children diagnosed with bipolar disorder (manic-depressive illness). Its interactive Web site, www.bpkids.org, was launched to coincide with publication of *The Bipolar Child: the Definitive and Reassuring Guide to Childhood's Most Misunderstood Disorder* (Broadway Books, 2000) by New York City psychiatrist Demitri Papolos, MD, and Janice Papolos, a journalist, both of whom are CABF board members. (*Medscape* 2000, para. 1)

While the original website address is now utilised by another group focused on weight loss, CABF has changed its name to the Balanced Mind Parent Network, and can be found online

listed as a program of the Depression and Bipolar Support Alliance (DBSA), (http://www.dbsalliance.org/site/PageServer ?pagename=bmpn_landing).

Apart from their website, the CABF also raised PBD awareness through a poster for school reception areas titled *"Just moody … or something more?"* (CABF 2007; Figure 4.11: CABF poster for school offices. (CABF, 2007)). This poster noted that PBD was: "Often dismissed as childhood defiance or ADHD" and if "left untreated … can lead to school failure, substance abuse and even suicide".

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Description: A poster image of a young boy looking distressed and text that reads "Just moody… or something more?" followed by a detailed description of the symptoms of "Paediatric Bipolar Disorder" grouped under "Mania" and "Depression", followed by the CABF logo and contact details.

CABF is currently known as the Balanced Mind Parent Network, and can be found online listed as a program of the Depression and Bipolar Support Alliance (DBSA) and can be found at the following link: http://www.dbsalliance.org/site/PageServer ?pagename=bmn_landing

Figure 4.11: CABF poster for school offices. (CABF, 2007)

Credibility of the CABF was further enhanced by mention of the:

> CABF's Professional Advisory Board [which included] experts Barbara Geller, MD, whose work is funded by the National Institute of Mental Health; Kay Redfield Jamison, PhD, a professor of psychiatry at John Hopkins Medical School; and

> Joseph Biederman, MD, a Harvard specialist on attention deficit hyperactivity disorder and bipolar disorder. (para. 6)

According to the *Medscape* online article, it actively promoted medication, suggesting:

> … treatment for early-onset bipolar disorder includes mood stabilizing medications such as lithium and anticonvulsants, and education and counselling for the whole family. "Children with bipolar disorder can learn to monitor their symptoms and eventually manage their medications when they grow up, just like kids with diabetes, epilepsy, and other chronic medical conditions," says Hellander. (para. 5)

The original CABF website had information for parents in an FAQ (Frequently Asked Questions) section, where descriptions of PBD included the following:

> Adults seem to experience abnormally intense moods for weeks or months at a time, but children appear to experience such rapid shifts of mood that they commonly cycle many times within the day. This cycling pattern is called ultra-ultra rapid or ultradian cycling …
>
> [PBD children tend to be] ... bossy, overbearing, extremely oppositional ... [their] mood can veer from morbid and hopeless to silly, giddy and goofy within very short periods of time. Some ... [display] social phobia, others … [can be] … extremely charismatic ...
>
> As babies [PBD were] ... extremely difficult to settle, rarely slept, experienced separation anxiety ... In early childhood [they are] ... hyperactive, inattentive, fidgety, easily frustrated and prone to terrible temper tantrums, especially if the word "no" appears in the parental vocabulary ... Rarely does the child show this side to the outside world. [www.bpkids.org/faq accessed mid-2007]

The CABF had encapsulated the 'narrow' and 'broad' PBD phenotypes into vignettes of childhood tantrum behaviour that could be applied to many, if not most, children by parents, particularly under stress. Over subsequent years, the organisation continued to actively promote the concept of childhood bipolar disorder to the public. Funding from pharmaceutical companies became an issue (Chapter 4.3.6).

In a 2003 special issue of the high-impact factor journal Biological Psychiatry, that was devoted almost entirely to PBD, there was an article by Martha Hellander, founder of the CABF. She described the CABF as comprising:

> [M]ore than 10,000-member families … many with several diagnosed children, illness in multiple generations, and even numerous sets of twins. Among these children is reported every comorbidity imaginable …" (Hellander 2003, p. 937)

She reported that 60% of the children with PBD in the organisation were "age 12 or younger" (p. 936).

Hellander, presumably along with many CABF parents, extolled the benefits of the "shift to the medical model" for diagnosing psychiatric illness in pre-pubertal children. She was critical of researchers "trained in psychodynamic theory, and invested in labelling psychosocial factors as the primary causes of behavioural problems in children", listing as unhelpful the "assumed psychopathology of mothers, … [and supposed influence of] poverty, divorce, or a 'disorganised home'" (p. 935). She indicated the CABF welcomed the growing emphasis on pharmacotherapy research and that "proposals and inquiries to the CABF Research Committee are encouraged" (p. 936).

The CABF were involved in the first major treatment guidelines article in *JAACAP* (Kowatch et al. 2005), and in fact, as the article's author statement indicated, the CABF co-sponsored it along with seven pharmaceutical companies:

> This project was sponsored by the Child and Adolescent Bipolar Foundation and supported by unrestricted educational grants from Abbott Laboratories, AstraZeneca Pharmaceuticals, Eli Lilly and Company, Forest Pharmaceuticals, Janssen Pharmaceutical, Novartis, and Pfizer. (Kowatch et al. 2005; p. 213)

4.3.4 **Books for parents and children 2000 to 2007**

Apart from Diler's book for fellow professionals, a multitude of books had been published for parents. The books were often written by PBD researchers and clinicians and included such titles (a far from exhaustive list) as:

- *Survival Strategies for Parenting Children with Bipolar Disorder.* (Lynn 2000)

- *Bipolar Disorders: A guide to helping children and adolescents.* (Waltz 2000)
- *Bipolar Not ADHD: Unrecognized epidemic of manic-depression in children.* (Isaac 2001; Figure 4.12: Bipolar Not ADHD: Unrecognized epidemic of manic-depression in children (Isaac 2001, front cover))
- *Raising a Moody Child: How to cope with depression and bipolar disorder.* (Fristad & Goldberg-Arnold 2003)
- *If Your Child is Bipolar: The parent-to-parent guide to living with and loving a bipolar child.* (Singer & Gurrentz 2003)
- *New Hope for Children and Teens with Bipolar Disorder.* (Birmaher 2004)
- *Parenting a Bipolar Child: What to do and why.* (Faedda & Austin 2006)
- *Bipolar Kids: Helping your child find calm in the mood storm.* (Greenberg 2007)

Removed due to copyright restriction.

See image of the book cover at this link:
https://www.iuniverse.com/en/bookstore/bookdetails/129489-Bipolar-not-ADHD

Figure 4.12: Bipolar Not ADHD: Unrecognized epidemic of manic-depression in children (Isaac 2001, front cover)

Paralleling the parents' self-help books were numerous books for children in picture bedtime story format. A short selection of titles includes:

- *Matt the Moody Hermit Crab.* (McGee 2002)
- *The Storm in My Brain.* (Joachim 2003)
- *Brandon and the Bipolar Bear: A story for children with bipolar disorder.* (Anglada 2004; Figure 4.13)

- *My Bipolar Roller Coaster Feelings Book* (Hebert 2005)
- *Darcy Daisy and the Firefly Festival: Learning about bipolar disorder and community.* (Lewandowski 2005)

Brandon and the Bipolar Bear (Anglada 2004) is quoted from at length as it likely describes a sequence that was repeated thousands of times. The cover is shown in Figure 4.13.

Removed due to copyright restriction.

See image of the book cover at this link:
https://www.booktopia.com.au/brandon-and-the-bipolar-bear-tracy-anglada/book/9780981739632.html?gclid=Cj0KCQiAqo3-BRDoARIsAE5vnaJSjDZjKzoM75XG9GsyJbBk2v9WksSd3kSvoojFehTag6J6d_p6PtAaAv46EALw_wcB

Figure 4.13: Brandon and the Bipolar Bear (Anglada 2004, front cover)

In this well-illustrated bedtime storybook, pre-pubertal Brandon at night feels lonely in his bed, has bad dreams, is irritated by the feel of a pyjama clothing tag, but eventually sleeps in so soundly he has to be woken by his mother shouting his name. When she tells him he has an appointment, he feels himself losing control of his anger, and in a fit of rage pulls his teddy bear's arm off. He falls sobbing to his knees in remorse and relates to the bear with the broken arm:

> Brandon rocked back and forth on the floor. "That's me," he said as the tears stung his eyes. "I'm broken, like the bear. Nobody can fix me." Then all was silent and empty inside.
>
> Brandon felt his mother wrap him in her arms. They rocked together for a while. She wiped his tears and picked up the bear. "We will fix this," she whispered. "I promise." "How mama?" asked Brandon.

Brandon's mother bandages the bear's arm back on, reminds Brandon that they are going to see Dr Samuel who will fix things, to which Brandon shouts "HOORAY! HOORAY!" as he

“zooms around the room” then bounces on his bed imagining he is a rocket that will blast off. At the appointment, Dr Samuel (Figure 4.14) tells Brandon:

> “You have bipolar disorder … Bipolar disorder can make your thoughts go too fast sometimes and too slow at other times … you might feel wonderfully happy, horribly angry, very excited, terribly sad, or extremely irritated all in the same day. It can be so confusing inside that living seems too hard.”

Removed due to copyright restriction.

Image Description: A page from the children's book 'Brandon and the Bipolar Bear'. At the top of the page the image of a smiling doctor. Below text describes Brandon's doctor's appointment. The doctor tells Brandon he has 'bipolar disorder'.

The book can be purchased at:

https://www.booktopia.com.au/brandon-and-the-bipolar-bear-tracy-anglada/book/9780981739632.html?gclid=Cj0KCQiAqo3-BRDoARIsAE5vnaJSjDZjKzoM75XG9GsyJbBk2v9WksSd3kSvoojFehTag6J6d_p6PtAaAv46EALw_wcB

Figure 4.14: Brandon and the Bipolar Bear (Anglada 2004, p. 16)

Brandon becomes tearful, agrees the description fits and says: “I think I got bipolar because I’m bad.” Dr Samuel reassures him that he is not alone, “maybe even a million other kids” have bipolar too, that it is genetically inherited and not because he is “bad”. Dr Samuel does give generic child psychiatric interventions: he indicates he will liaise with Brandon’s therapist and school and asks Brandon to promise to inform his mother if he feels like hurting himself. But the message to Brandon is clear: his moods are not fully controllable but are neurochemical and requiring of a pharmacotherapeutic fix. The back cover has review quotes, firstly from Janice Papolos:

> "The comforting explanation of bipolar disorder that Dr. Samuel gives him makes Brandon feel not alone, not bad, but hopeful that the medicines will make him (and his Bipolar Bear) feel better. We were so moved by the power of this little book and we feel better that we now can highly recommend a book for children ages 4 through 11."

Secondly, from the CABF:

> "Readers learn about Brandon's symptoms, fears, and treatment from a child's viewpoint. One of our children, age 7, wouldn't part with it. Suitable for ages 4-10 but can also serve as a tool for improving communications with siblings, teachers, and friends."

Anglada has since written several other books and has a user-friendly website http://www.bpchildren.com/ that provides a wide variety of resources for parents, children and teens, from colouring in sheets featuring Brandon's Bipolar Bear, to *Tips for Kids by Kids* with bipolar disorder.

In *My Bipolar Roller Coaster Feelings Book* (Hebert 2005), pre-pubertal Robert narrates his story. See Figure 4.15.

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Image Description: Two pages from children's book 'My Bipolar, Roller-Coaster, Feelings Book' by Bryna Hebert. The first page has an image of a mother and child with speech bubbles beside their heads. The mother's speech bubble reads 'Not today.' And the child's reads 'Please Mom!'. The text below reads 'Have you ever asked your mother for candy at the grocery store and had her say "no"? The last time it happened to me, I couldn't get the candy out of my head, I wanted it so much.'

The second has an image of a girl smiling and a boy backflipping. It compares their expressions of happiness; other children smile and have a 'twinkle in their eye' whilst the bipolar protagonist of the book giggles and wants to do 'backflips'.

The book can be purchased at:
https://www.ebay.com.au/itm/My-Bipolar-Roller-Coaster-Feelings-Book-by-Bryna-Hebert/184195346081?hash=item2ae2e5eea1:g:CcwAAOSwRGJeXdfr&frcectupt=true

Removed due to copyright restriction.

Image Description: Two pages from children's book 'My Bipolar, Roller-Coaster, Feelings Book' by Bryna Hebert. First page continues the candy story from above and reads 'I got so mad!! I even threw the bag of candy at my mom. We had to leave the store. Mom calls it a rage when I do that. She says I can't go shopping with her for a while, until I feel better. I feel bad because I embarrassed my mom in front of all those people.'

The second pages shows a child scared under his blanket. 'When the lights go out at night. I don't just get a little scared, I get terrified! I can't help it. My brain goes in fast motion, like a movie in fast forward and I can't stop it.'

The book can be purchased at:
https://www.ebay.com.au/itm/My-Bipolar-Roller-Coaster-Feelings-Book-by-Bryna-Hebert/184195346081?hash=item2ae2e5eea1:g:CcwAAOSwRGJeXdfr&frcectupt=true

Figure 4.15: *My bipolar roller coaster feelings book* (Hebert 2005, pp. various)

As can be seen, Robert is an active child some of the time which is referred to as “bouncing off walls” by his parents and being “silly, giddy and goofy” by “Dr Janet.” When he asks his mother for candy at the grocery store, he says “please”. However, when she replies: “not today,” he loses his temper and throws candy at her. This leads to them leaving the store and he feels bad for publicly embarrassing his mother. Later that night he cannot sleep as he ruminates on the day’s events. He describes being terrified in the dark and his “brain goes in fast motion, like a movie in fast forward, and (he) can’t stop it.” By the end of the book he is accepting of his diagnosis, his father likens it to other children having asthma, and he is drawn with a handful of pills and suitably sedated facial expression (Figure 4.16).

Removed due to copyright restriction.

Image Description: Page 23 of 'My bipolar, roller-coaster, feelings book' which reads 'I don't like having bipolar disorder, but I can't change that. I also don't like having to take all those pills, but, the bad nightmares have gone away and they help me have more good days. Dad says a lot of kids have things wrong with their bodies, like asthma and diabetes, and they have to take medicine and be careful too. I guess I'm not the only one.' In the picture, Robert has a resigned facial expression and six pills in his hand.

The book can be purchased at:
https://www.ebay.com.au/itm/My-Bipolar-Roller-Coaster-Feelings-Book-by-Bryna-Hebert/184195346081?hash=item2ae2e5eea1:g:CcwAAOSwRGJeXdfr&frcectupt=true

Figure 4.16: *My bipolar roller coaster feelings book* (Hebert 2005, p. 23)

These books expressed to children that moods of joyful abandon or silly joking, if perceived by adults as excessive and troublesome, could in fact be brief manic episodes driven by abnormal neurochemistry. This label could also be applied to their anger, rage, or oppositional response to not getting their way. Additionally, anxious ruminations in the setting of guilt and separation-anxiety relating to disruption to their primary attachment relationships could be interpreted as the racing thoughts of mania. Feeling sad and distressed for a few hours with negative self-attributions and passing suicidal thoughts could be signs of clinical depressive episodes.

The answer given to these 'mood swings' is pharmacological sedation. However, for the children there is the problem of 'labelling'. Henceforth their sense of self and ownership of their emotions and actions becomes suspect to whether it is their PBD, their medication, or their true self. Their own and others' expectations and hopes for their futures may be curtailed by the diagnosis. As implied in the *JAACAP* treatment guidelines of Kowatch et al. (2005), the PBD diagnostic label does come with an implied message of disability that may well bring grief: "It is important for clinicians to be sensitive to and help parents through the process of grieving the loss of their healthy child" (p. 219). This iatrogenic effect of labelling is further explored in Chapter 9.2.3.

For many parents the plethora of such books, written by experts, are likely to have been reassuring and offered a straightforward explanation and solutions to daily parenting

problems, addressing the substantial needs of parents struggling with very difficult behaviour coming from their children.

4.3.5 **Book: Is your child bipolar?**

This emphasis on medication as first line treatment of postulated cases of PBD was continued in a best-selling book for parents, *Is Your Child Bipolar?* (McDonnell & Wozniak 2008). Professor Wozniak is a senior researcher with the MGH-Harvard group, and she praised her mentors including Professor Biederman, noting the controversy raging over PBD by this time. She also disclosed her own childhood with a mother diagnosed with schizophrenia, but whom she now suspects had bipolar disorder, as a driving factor:

> Dr. Joseph Biederman … is well known for his vast knowledge, clinical wisdom, and intellect … He helped free me from the previously taught notion that "children don't get bipolar disorder," so that I could truly hear what parents and children were describing.
>
> I watched my mother be disabled and shamed by her psychiatric symptoms. Without that truly awful and traumatic experience, I doubt I would ever have become a psychiatrist at all. Any help I bring is a legacy to her suffering. (p. xv)

In helping parents answer the question of "Is your child bipolar", McDonnell and Wozniak list the features in a table (p. 11-12) that has such claims as: Bipolar disorder is "a brain disorder" or "illness" "that children, including very young children, can develop." It is "more common than most people realise" with "three-quarters of a million children with full-blown bipolar, plus two to three million on the bipolar spectrum, plus one and a half million with depression who will develop bipolar by the time they're adults." In total, that is around five million US children and teens allegedly affected before adulthood. The broad phenotype is outlined: "rapid cycling and mixed mood states are the rule; classic adult-style mood cycles are the exception. The number one symptom of mania is extreme irritability, not euphoria." Sudden onset and offset of symptoms may be environmentally mediated: "Your child's symptoms might show up at home but not school, or be worse at the grocery store, or be unpredictable."

The book has extensive sections on the mood stabilizers lithium and anticonvulsants, atypical antipsychotics and other psychotropics. A section titled "Polypharmacy or combined

pharmacotherapy" states: "In rare but severe cases, some take as many as a dozen different medications. This can be disconcerting to people … But in many cases, polypharmacy is appropriate and necessary for effective treatment" (p. 165).

There are sections on psychotherapy, family therapy, and parenting strategies as well as electroconvulsive therapy, transcranial magnetic stimulation and various nutritional supplements. However, as a member of the FCAP of the RANZCP with training in an adult psychiatric asylum, the book left me disconcerted in that the description of treatments parallel those reserved for adults with severe treatment-resistant bipolar disorder or melancholic depression. This sentiment is shared by several US colleagues; for example, Levin states in a review of the book: "Sadly, in the end, the question might not be, is your child bipolar? but is your child psychiatrist wrong?" (Levin 2010, p. 373). He highlights the lack of consideration of developmental trauma: "the book makes only 5 indexed references to trauma. And the authors define PTSD simply as '… an anxiety disorder related to a specific incident' (p. 26). There is no mention of Developmental Trauma Disorder (van der Kolk, 2005)" (p. 371).

4.3.6 **Pharmaceutical industry sponsorship of the CABF**

Questions were raised over conflict of interest issues regarding the CABF due to pharmaceutical industry funding. The CABF's position appeared to have discrepancies on the organisation's website. On one webpage (accessed in February 2013, no longer available as of 29 August 2013), http://www.bpkids.org/site/PageServer?pagename=lrn_testimony, the executive director of the CABF is quoted testifying to an FDA committee that the CABF does not receive pharmaceutical industry funding:

> CABF Testimony at the June 9, 2009 Meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration
>
> Concerning new drug approvals for Seroquel for schizophrenia (children ages 13-17) and bipolar disorder (children ages 10-17); Geodon capsules for bipolar disorder (children ages 10-17); and Zyprexa for schizophrenia and bipolar in adolescents.

> "My name is Susan Resko and I am the executive director of the Child & Adolescent Bipolar Foundation. I represent over 25,000 constituents; 95% are parents of children living with bipolar disorder and related conditions. CABF neither seeks, nor accepts financial support from pharmaceutical or medical device companies."

However, from the CABF's 2006 financial disclosure pdf document on the same website (accessed in February 2013, but since removed) www.bpkids.org/site/DocServer/CABF_2005-06_Audited_Financials.pdf?docID=1041:

> The Foundation revenue is comprised primarily of donations from individuals and grants received from Pharmaceutical companies.
>
> … For the year ended June 30, 2006, grants received from one pharmaceutical company comprised more than 10% of total support and revenue.
>
> … During fiscal years 2005 and 2006, the foundation, which had historically received 50-70% of its funding from the pharmaceutical industry.

The contradiction between the two sets of statements was criticized on a number of public internet blogs (e.g. ("Stan", 2009) where Resko's testimony to the FDA is recorded). The renamed CABF website, The Balanced Mind Foundation, did give financial statements for the years from 2007 onwards as late as 2013. As of February 2018, they do not give public statements (http://www.dbsalliance.org/pdfs/devo/RecordsRetentionPolicy.pdf). When still publicly available the statements indicated that there was still pharmaceutical industry financial sponsorship although reduced after 2006. The organisation has looked elsewhere for funding, including corporations like PepsiCo Inc. The foundation was successful in winning $250,000 sponsorship from PepsiCo Inc. in 2011 with support from the Chicago Bears American Football team (Resko 2011a).

4.3.7 **Summary**

The CABF and JBRF were US-based organisations. They linked many of the leading PBD researchers to a passionate advocacy group of up to 25,000 parents, and through their websites, online diagnosis questionnaires and facilitating some of the genre of books for clinicians, parents and children, helped to market the PBD hypothesis as a newly recognised common diagnosis. Such well-meaning passion and intentions were to a large extent funded

by pharmaceutical companies, who, as was indicated in Chapter 4.2, were keen to find new markets for their on-patent atypical antipsychotics. The lack of similar organisations internationally may have been a contributory factor to the PBD epidemic remaining mostly a US phenomenon.

4.4 PBD in the US public media to 2006

In the first decade after PBD was defined by the WUSL and MGH-Harvard researchers the US media generally reported PBD as an advance in mental health, the recognition of a previously under-recognised disorder, as per the following examples. The influence of this positive coverage presumably contributed to the huge rise in PBD diagnosis and treatment of children in the US – whilst there was little evidence of contemporaneous diagnosis of this disorder outside the US. After the death of Rebecca Riley in late 2006, the media began to report conservative views, critical of the PBD diagnosis, including covering the Grassley Inquiry in 2008 (Chapter 4.8). Below is a description of media coverage preceding Rebecca Riley's death.

4.4.1 PBD on *The Oprah Winfrey Show*, 2000

In February 2000, *The Oprah Winfrey Show*, in an episode titled "Explosive Children", interviewed a Dr Ross Greene, author of a book by the same title. Oprah also interviewed Demetri and Janice Papolos, who co-authored the run-away best-seller *The Bipolar Child* and set up the Juvenile Bipolar Research Foundation (JBRF; www.jbrf.org). The segment featured several mothers in the audience and video clips of their children engaged in severe tantrums. All appeared to be patients of Dr Papolos. However, my observation on watching the episode years later (URL: http://www.oprah.com/oprahshow/Advice-for-Parents-of-Explosive-Children; actual video unavailable since 2013) was that tantrum behaviours were being described as 'childhood manic depression'. It was even noted that one boy never displayed the same behaviour at school "where he was always an angel". Interestingly, the link at Oprah.com as of September 2013 simply mentions the Papoloses and their book by name, but then only quotes Dr Greene about managing rages. Parental comments (to 2011, since deleted) on the webpage used phrases like "bipolar kids."

4.4.2 **PBD in *The New York Times*, 2000**

The New York Times, like the rest of the media, was fairly accepting that a new disorder had been discovered, although later it would publish a series of sceptical articles by investigative journalists examining conflict of interest relationships between the pharmaceutical industry and prominent PBD researchers. An article in 2000 (*The New York Times* 2000) questioned the medicating of young children but not so much the new disorder:

> Medical science long believed that mental illnesses such as depression and bipolar disorder began after childhood. Now it is known that such disorders can begin in early childhood, with an estimated six to nine million children and adolescents currently suffering from serious conditions. Failure to treat mental illness in young children can have serious, lifelong consequences. But the difficulty lies in accurately diagnosing disorders in the very young and determining when medication is appropriate. (para. 3)

4.4.3 **TV advertising during cartoons, 2001**

The MGH-Harvard group advertised on a children's cartoon TV station asking for research subjects in 2001 featuring a restless child in his children's car seat. The advert is still available in early 2019 on YouTube at https://www.youtube.com/watch?v=RGkQdzU2DOk. The transcript of the advert could have appealed to many parents who struggled with children with disruptive behaviour and moodiness:

> (father) *Our problems started when he was 4 years old.*
>
> (mother) *No day care could handle our son, he was just too…*
>
> (another mother/ or child care worker) *too violent and unpredictable, I had to protect the other children from his…*
>
> (young male doctor) *his outbursts, mood swings – I see a LOT of cases like this.*
>
> (preschool boy wriggling in car seat, adult older male voice over) *Your child may be facing a chemical problem that you can't manage without help. If you or someone you know is living with bipolar disorder call us to participate in our research study*. (phone number on screen)

(mother) *Heart-breaking. No-one understands the pain!*

(older male voice over, logo of 'Mass-General Children's Hospital – Bipolar Research Study' and phone number) *We're Mass General. We can help.*

The advertisement is undergirded by the validity of the PBD hypothesis. The advert was run on the "Toon" cartoon network, during "Outlaw Star", a Japanese sci-fi action warfare cartoon likely to appeal to energetic boys who in turn were likely to fit the demographics of the MGH-Harvard research and clinical cohorts. It is difficult to imagine such an advert on European or Australasian television: a probable contravening of ethical standards with objections from professional child psychiatry and paediatric bodies, due to majority non-acceptance of the PBD hypothesis, would possibly prevent this. As such, it is another example of how the media came to influence the spread of the PBD hypothesis in the US in particular.

4.4.4 *TIME* magazine article 2002

Further credibility for the PBD hypothesis came from a cover story "Young and Bipolar" in *TIME* magazine (Kluger & Song 2002; Figure 4.17). The *TIME* article described a 16-year-old girl who may well have suffered from real bipolar disorder, a 9-year-old boy with oppositional behaviour, and interviewed a single mother of three whose 5-year-old and 2-year-old had both been diagnosed with PBD.

Removed due to copyright restriction.

Cover of *TIME* magazine with a picture of a young boy and text reading 'Inside the Volatile World of the YOUNG AND BIPOLAR: Why are so many kids being diagnosed with the disorder once known as MANIC DESPRESSION?'

Image can be seen at this link: http://content.time.com/time/covers/0,16641,20020819,00.html

Figure 4.17: Cover of *TIME* Magazine August 19, 2002

Papolos was quoted extensively:

> Most children with the condition are ultra-rapid cyclers, flitting back and forth among mood states several times a day. Papolos, who co-wrote *The Bipolar Child*, studied 300 bipolar kids ages 4 through 18, and he believes he has spotted a characteristic pattern. In the morning, bipolar children are more difficult to rouse than the average child. They resist getting up, getting dressed, heading to school. They are either irritable, with a tendency to snap and gripe, or sullen and withdrawn.
>
> By midday, the darkness lifts, and bipolar children enjoy a few clear hours, enabling them to focus and take part in school. But by 3 or 4 p.m., Papolos warns, "the rocket thrusters go off," and the kids become wild, wired, euphoric in a giddy and strained way. They laugh too loudly when they find something funny and go on long after the joke is over. Their play has a flailing, aggressive quality to it. … Such wildness often continues deep into the night—which accounts in part for the difficulty they have waking up in the morning. "They're like Dr. Jekyll and Mr. Hyde," says Papolos, "which is how their parents describe them." (para. 15-16)

The *TIME* article concluded by inferring the early developmental origins of PBD as far back as in-utero:

> Preverbal toddlers and infants cannot manifest the disorder so clearly, and there is no agreement about whether they exhibit any symptoms at all. However, many parents of a bipolar say they noticed something off about their baby almost from birth, reporting that he or she was unusually fidgety or difficult to soothe. Broman insists she knew her son Kyle was bipolar even when he was in the womb. "This child never slept inside," she says. "He was active 24 hours a day." (para. 17)

This article, like the *Oprah Winfrey Show* episode, gave the PBD hypothesis widespread prominence, and brought PBD to the attention of me and my colleagues here in Australia.

However, the media changed its approach to become more sceptical and involve investigative journalism, following the tragic death of an ADHD/PBD-diagnosed 4-year-old girl in Massachusetts from her psychotropic medication in December 2006.

4.4.5 **A tragedy unfolds …. the death of 4-year-old Rebecca Riley**

In late 2006, a 4-year-old Boston girl's death was reported as related to her psychotropic medications. She had been diagnosed with ADHD at age 28-months and comorbid PBD five weeks after her third birthday. This tragic event had many consequences. One significant outcome was that the US media began to dramatically change its stance towards the PBD hypothesis.

According to police reports (Pringle 2007) Rebecca was on a regime of clonidine (an alpha 2-adrenergic agonist sedative) at 50 micrograms three times per day, plus 200 micrograms nocte, sodium valproate (an anticonvulsant mood stabiliser) at three capsules (dose not reported) morning and night, and quetiapine (an atypical antipsychotic) at 25mg morning and 175mg night at the time of her death. These are high doses for a small girl. It was reported that she had a respiratory infection and her parents had given her decongestants (that may have interacted with her psychotropic medication) and extra clonidine as they saw it as her sleeping medication. *The Boston Globe, The Patriot Ledger* and *The New York Times* as well as several freelance investigative journalists all gave the story extensive coverage, and her photograph (Figure 4.18) was widely published (e.g. nbcnews.com 2007).

Removed due to copyright restriction.

Image description: portrait of Rebecca Riley.

Image can be seen at this link: https://www.findagrave.com/memorial/24724490/rebecca-jeanne-riley

Figure 4.18: Rebecca Riley, 4, died Dec. 13, 2006, in Hull, Mass. Rebecca's parents, Michael and Carolyn Riley, are accused in the drug-poisoning death. (nbcnews.com, 23 March 2007, http://www.nbcnews.com/id/17758170/ns/health-childrens_health/t/girls-death-stirs-debate-over-psychiatric-meds/#.XTLcPS1L3xU)

The critical finding stated in the coroner's report indicated she had suffered long-term effects from polypharmacy (Pringle 2007):

> [T]he official autopsy report says Rebecca died of the "combined effects" of the drugs, and that her lungs and heart were damaged by "prolonged abuse of these prescription drugs, rather than one incident." (para 29)

Rebecca's parents were charged with first-degree murder. *The Boston Globe* stated: "prosecutors say they killed their daughter by regularly giving her drug overdoses, ostensibly to keep her calm and help her sleep" (Cramer & Mishra 2007).

The family lived in the Boston region of Massachusetts and the child psychiatrist treating Rebecca, Dr. Kayoko Kifuji of Tufts-New England Medical Center, had emigrated from Japan to complete her psychiatric training. Kifuji denied any wrongdoing and alleged that Rebecca's mother had escalated the clonidine dose from 2 to 2½ tablets at night without permission (Kowalczyk 2007). An accompanying article (*The Boston Globe* 2007) listed numerous child protection notifications and noted a therapist working with Rebecca and her 6-year-old sister had expressed concerns regarding overmedication and child abuse by the father. An older half-sister (not the father's biological daughter) had been removed from the home (Cramer

2007) due to allegations of sexual abuse by Rebecca's father and he had been reported for physically abusing the 11-year-old brother still at home. The Department of Social Security had investigated the allegations of overmedicating but could not find child psychiatrists who would comment: "'our interpretation of their explanation was that there was a reluctance to engage in second-guessing of fellow professionals,' Spence (local DSS director) told the Globe" (para. 16). *The New York Times* (Carey 2007b) reported solid support for the psychiatric treatment provided to Rebecca Riley, from the psychiatrist's institution:

> Tufts-New England Medical Center, where the child was treated, released a statement supporting its doctor and calling the care "appropriate and within responsible professional standards." (para. 10)

The CBS television *60 Minutes* investigative program covered the tragedy (Chapter 4.6.2) and reported Tufts-New England Medical Center issued the exact same statement about Rebecca Riley's treatment (*60-Minutes* 2007; transcript para. 14).

Dr Kifuji's lawyer defended her practice as based on the accepted model of care of the local MGH-Harvard PBD researchers. As reported in *The Boston Globe (*Allen 2007):

> Riley's psychiatrist has said she was influenced by the work of Biederman and his protégé, Dr. Janet Wozniak. They are by far the leading lights in terms of providing leadership in the treatment of children who have disorders such as bipolar," said J. W. Carney Jr., lawyer for Dr. Kayoko Kifuji … "Dr. Kifuji subscribes to the views of the Mass. General team." (para. 4 & 5)

One report indicated all three children still at home, as well as the father and maternal grandmother, were diagnosed with bipolar disorder. According to testimony in court, Rebecca's 6-year-old sister was diagnosed at age 2, "following the family's first 10-minute consultation with Kifuji in April 2003" (para. 9). It was reported that Kifuji based the sister's bipolar diagnosis on maternal reports of aggression and that the 2-year-old was complaining of seeing "monsters and ghosts" (Kelly 2010). Kifuji was granted immunity from prosecution in order to testify in the parents' murder trial, set for 2010 (Chapter 4.6.3)

4.6 **PBD in the US media after death of Rebecca Riley**

4.6.1 **Introduction**

The reporting through 2007 into 2008 of the young girl's tragic death and the subsequent murder trial of her parents, particularly in *The Boston Globe*, *The New York Times*, *The New Yorker*, *USA Today*, *CBS*' television program *60 Minutes* and later *Public Broadcasting Service (PBS)*'s documentary *The Medicated Child* (2008), all permitted the airing of topics related to the PBD hypothesis and epidemic that had been mostly muted in the academic literature to that point in time.

Several themes emerged as child and adolescent psychiatrists, adult psychiatrists, paediatricians, psychologists and others went on public record. The relevance of these statements in the media frames the peer-reviewed literature, that, reliant on data-driven research, may have not allowed US clinicians and researchers who were sceptical of the PBD hypothesis, and hence lacked data, to fully express their views. Although the media is generally not a source of unbiased news, nor the best venue for scientific debate, published sceptics such as Carlson and McClellan were more forthright when interviewed by the media, and other clinicians found an avenue to express their opinion. In the relative absence of debate in the peer-reviewed literature, both pro-PBD and sceptical views were expressed in the media. As this thesis strives to incorporate a history of the PBD phenomenon, the strident and detailed nature of the public debate gives insights into the phenomenon and is covered here in some depth.

The themes covered the iatrogenic effects of psychotropic medication for children and investigative journalism looked into the FDA's adverse events data to find that Rebecca Riley was not an isolated victim. Other topics aired included the biomedical reductionist paradigm surrounding the PBD diagnosis, the neglect of maltreatment factors, 'diagnostic upcoding' in the US managed care health system, the influence of the pharmaceutical industry and conflicts of interest issues involving key PBD researchers.

4.6.2 **CBS *60 Minutes* presents 'Bipolar: Dangerous Diagnosis?'**

The US CBS television station covered PBD on its popular *60 Minutes* current affairs program (*60 Minutes* 2007). The segment was titled *What killed Rebecca Riley? Bipolar: Dangerous diagnosis?* The program originally aired on 30 September 2007. The program webpage was updated in 2009 and dropped the contentious "Bipolar: Dangerous Diagnosis?" phrase. The 15-minute video now requires subscription https://www.cbsnews.com/video/what-killed-rebecca-riley/, although a transcript is available at https://www.cbsnews.com/news/what-killed-rebecca-riley/. Several key points are summarised here.

The program interviewed Carolyn Riley in jail. She had thought her daughter was on a lot of pills but "trusted the doctor" and gave extra bedtime clonidine because Rebecca couldn't sleep. Poignantly, when asked if she thought Rebecca really had bipolar disorder, she said "Probably not … I don't know. Maybe she was just hyper for her age" (p. 3, para. 18, 20).

The program interviewed Professor Biederman on the increased diagnosing of PBD and his group's role. He responded:

> The idea is rare if you define it in very strict ways. Our contribution has been to describe the many ways that this condition may emerge in children that may make it a little bit more diagnosable and less rare … The average age of onset is about four, it's solidly in the preschool years. (p. 2, para. 3, 6)

Although this was a confident statement, he conceded that the research was not yet conclusive:

> Yes. I recognize the fact that we have a gap in knowledge," Biederman says. "But the patients that come to me, and the families in tears and despair with these type of problems, I in good faith cannot tell them, 'Come back in ten years until we have all the data in hand.' I still need to use medicines that I am assuming that if they work in adults, with appropriate care and supervision, may also work in children. (p. 3, para. 2)

Many child psychiatrists both within the US and outside its boundaries would take exception to Professor Biederman's statements. Their views were encapsulated in McClellan's 2005 commentary to the PBD treatment guidelines article of Kowatch et al. (2005) and supported

by diagnostic rates and findings in longitudinal offspring studies (Chapter 4.8.7) as well as academic opinion in most nations (Chapter 7). Similar phenomenology expressed by some children and families is likely to be universal or at least common to all countries. Many clinicians in child psychiatry and paediatrics, both in the US and internationally, would make, based on their training, a biopsychosocial diagnostic formulation, taking into account the context of the family's psychosocial stressors and impact of parenting style and family dynamic issues, as well as neurodevelopmental issues that may be present. This point is elaborated in Chapter 9.4. What families need, and generally appreciate, is an honest dialogue about the nature of their child's behaviour and all contributing factors. Further, ethical practice involves an honest discussion of the role, adverse effects and limitations in knowledge of pharmacotherapy, as a part of a wider treatment program.

This view was expressed by McClellan, whom *60 Minutes* also interviewed; he expressed strong scepticism about PBD, pointed to the non-specific symptoms, and said children admitted to his Seattle inpatient unit were taking an average of four psychotropic drugs: one had been on 12 psychotropics concurrently. *60 Minutes* interviewed a family whose primary-school-age son was taking several psychotropics for PBD diagnosed at 4-years-old. In the Seattle unit the boy was re-diagnosed with ADHD and discharged on appropriate stimulant medication. McClellan stated:

> The problem is symptoms like irritability or recklessness or high energy when you're an eight-year-old don't necessarily predict in the long run developing bipolar disorder. Some might. Do you expose all those kids to medications to prevent the one kid that's going to get it? (p. 2, para 21)

4.6.3 **2010 Trial and sentencing of Rebecca Riley's parents**

Both of Rebecca's parents were remanded without bail in February 2007. In addition to the charges of dispensing extra clonidine, it was reported that prosecutors alleged that Rebecca's father sought psychiatric diagnoses for his children to gain increased family welfare payments, but these were only granted for the older two siblings and hence there was motive for murder in Rebecca's case (Kelly 2010). In 2010 Rebecca's father, Michael Riley, was convicted of first-degree murder and sentenced to life without parole, and her mother,

Carolyn Riley, was convicted of second-degree murder and received a life sentence with possibility of parole after 15 years.

The estate of Rebecca Riley filed a civil suit against Dr Kifuji and Tufts Medical Center who in 2010 settled out of court for $2.5 million that the estate would direct towards Rebecca's sister and brother. As part of the settlement it was reported (Lambert 2011) that Tufts Medical Center:

> [A]greed to start an awareness program, so young doctors know the dangers of over-prescribing such drugs. Tufts declined comment on that but said the hospital will be looking for ways to expand education programs for caregivers who treat "psychiatrically ill children in troubled homes." (para. 9)

The Boston Globe (Wen 2011) reported that:

> [M]any in the medical and legal community questioned why Kifuji was not held criminally accountable. When Rebecca died, Kifuji was the psychiatrist for all three Riley children, diagnosing each with ADHD and bipolar illness and prescribing similar mood-altering drugs. (paragraphs 8 -9).

4.6.4 **Morbidity and mortality from psychotropics among US Children**

Rebecca Riley was not the only child who received media attention due to deleterious effects of psychotropic medication prescribed for PBD. Also reported was Destiny Hager, a 3-year-old PBD-diagnosed toddler who died of faecal impaction secondary to atonic bowel from adult doses of two atypical antipsychotics (quetiapine and ziprasidone) in Kansas (Carpenter 2009).

Both *USA Today* and *The New York Times* independently researched the US Food and Drug Administration (FDA)'s Adverse Event Reporting System (FAERS). FAERS is rather unwieldy to research, but the investigative journalism of *USA Today* (Elias 2006) reported:

> A *USA TODAY* study of FDA data collected from 2000 to 2004 shows at least 45 deaths of children in which an atypical antipsychotic was listed in the FDA database as the "primary suspect". There also were 1,328 reports of significant side effects, some of them life-threatening.

> Studies suggest the FDA's Adverse Events Reporting System database captures only 1% to 10% of drug-induced side effects and deaths, "maybe even less than 1%," says clinical pharmacologist Alastair J.J. Wood, an associate dean at Vanderbilt Medical School in Nashville. So the real number of cases is almost certainly much higher. (para. 10-11)

The article reported 41 cases of the life-threatening neuroleptic malignant syndrome. They also reported:

> Among the 45 pediatric deaths in which atypicals were the primary suspect, at least six were related to diabetes: atypicals carry warnings that the drugs may increase the risk of high blood sugar and diabetes. Other causes of death ranged from heart and pulmonary problems to suicide, choking and liver failure.
>
> An 8-year-old boy had cardiac arrest. A 15-year-old boy died of an overdose. A 13-year-old girl experienced diabetic ketoacidosis, a deficiency of insulin.
>
> More than half of the kids who died were on at least one other psychiatric drug besides the atypical antipsychotic, and many were taking drugs for other ailments.
>
> The youngest, a 4-year-old boy whose symptoms suggested diabetes complications, was taking 10 other drugs. (para. 27-30)

Deaths in cases of Type-I diabetes may not have been related to the atypical antipsychotics, but Type-II diabetes can occur in children on atypical antipsychotics and the reports are highly concerning. Not only were young children reported as dying from the effects of PBD medication, many others suffered extreme side effects. The *USA Today* article described a case of tardive dyskinesia in a 13-year-old boy:

> Rex Evans' parents are bitter about what happened to their son. They believe the 13-year-old Colorado Springs boy was harmed permanently by an atypical antipsychotic he took several years ago. Rex now has a serious case of tardive dyskinesia (TD), suffering daily episodes of involuntary jerking movements and facial grimacing, says Erin Evans, his mother. (para. 14)

Supporting this journalistic review of widespread extrapyramidal side-effects (EPSE), formal research into the widespread prescribing of psychotropics to Texan foster children found 430

children in 2004 “were prescribed antidyskinetic drugs to control side effects from antipsychotics” (Strayhorn 2006).

The New York Times undertook similar research to *USA Today* on two occasions and reported that in 2006 alone (Harris, G, Carey & Roberts 2007):

> [T]he FDA received reports of at least 29 children dying and at least 165 more reports of other serious side effects in children where an antipsychotic was listed as the "primary suspect”. That was a substantial jump from 2000, when there were at least 10 deaths and 85 serious side effects among children linked to the drugs. Since reporting of bad drug effects is mostly voluntary, these numbers likely represent a fraction of the toll. (para. 64)

They reported a girl with tardive dystonia in her back muscles persisting long after ceasing risperidone:

> Anya gained weight but within two years developed a crippling knot in her back. She now receives regular injections of Botox to unclench her back muscles. She often awakens crying in pain (para. 2).

A later article (Harris, G 2008a) reported: “From 1993 through the first three months of 2008, 1,207 children given Risperdal suffered serious problems, including 31 who died” (para. 18) and cited a paediatric neurologist and FDA committee member:

> Dr Dure said he was concerned that doctors often failed to recognize the movement disorders, including tardive dyskinesia and dystonia, that can result from using these medications. (para. 21)

These findings by investigative journalists at two major US news media have since been supported by the peer-reviewed literature. While atypical antipsychotics are marketed as causing few EPSE, research suggests the actual rate in children and adolescents is substantial. For example, a 6% rate of tardive dyskinesia was found in a cohort of 5 – 18-year-olds on atypical antipsychotics for six months or longer (Wonodi et al. 2007). In Texas during fiscal 2004, 430 foster children “were prescribed antidyskinetic drugs to control side effects from antipsychotics” (Strayhorn 2006, p. vii & p. 77) and a meta-analysis of EPSE from atypical antipsychotics in the paediatric age range (Pringsheim et al. 2011) reported an odds ratio of

3.55 above placebo for risperidone and 3.70 for aripiprazole, with 27% of adolescents in olanzapine trials requiring anticholinergic antidyskinetic drugs. A review (Panagiotopoulos et al. 2010) of the metabolic effects of atypical antipsychotic drugs in children and teens found that this younger age cohort were more susceptible to rapid weight gain, increase in waist circumference and abdominal adiposity than adults and insulin resistance, diabetes, dyslipidaemia and hepatic dysfunction all occur in the paediatric age range.

The research of the FAERS by *USA Today* and *The New York Times* journalists had used comparable methodology to an *Archives of Internal Medicine* article by Moore TJ, Cohen and Furberg (2007). Moore et al. found several atypical antipsychotics rated in the top 15 as 'primary suspect' for cause of death amongst all medications on the FAERS database. In email communication with Harris of *The New York Times* and Thomas J Moore, lead author of the *Archives of Internal Medicine* study and researcher at the Institute for Safe Medication Practices, Huntingdon Valley, Pennsylvania, both indicated that they had essentially used the same research methodology (G Harris, 2007, email, 19 September; T J Moore, 2007, email, 1 November). Moore said his group had not examined the FAERS data base by age but thought the figures quoted in the media were probably correct. Moore wrote in his email:

> [W]e did not analyze in this study the morbidity and mortality from specific drugs by age group. ... I would suspect (but do not know) that psychoactive drugs (mainly stimulants, antidepressants and antipsychotics) account for a very substantial fraction of serious injuries and deaths in the 5-17-year-old age group. I would not be shocked if they accounted for a majority of events.

Recent research supports Moore's concerns. A study of all 5 – 24-year-olds Medicaid recipients prescribed atypical antipsychotics in Tennessee from 1999 through 2014 found a hazard ratio for mortality not due to overdose of 4.29 over those not prescribed atypical antipsychotics. The increased mortality was attributed to sudden cardiac arrest from QTc prolongation and metabolic adverse effects (Ray et al. 2019). These iatrogenic consequences from psychotropic medications are discussed further in Chapter 9.2.2.

4.6.5 **Concerns regarding medication**

The media allowed for a frank debate about the role of psychotropic medication in paediatrics and psychiatry. Hyman, a Harvard professor of psychiatry and former director of the NIMH,

was quoted in *The New Yorker*: “The diagnosis [PBD] has spread too broadly, so that powerful drugs are prescribed too widely … We are going to have hell to pay in terms of side effects” (Groopman 2007, p. 30), and later in *The Boston Globe*:

> We don't know the first thing about safety and efficacy of these drugs (Zyprexa, Risperdal and Seroquel) even by themselves in these young ages, let alone when they are mixed together," said Dr Steve Hyman. (Allen 2007, para. 29)

Further articles in the Boston press quoted other local paediatricians and psychiatrists:

> "Having a 4-year-old on [those] three medications and the intensity of the medications, I'd have big concerns,” said Dr. Candida Fink, a child psychiatrist who specializes in bipolar illness. “These are big-gun medications.”
>
> … Dr. Eli Newberger, pediatrician and specialist on child abuse, who joined several other physicians in questioning how a 4-year-old girl could be given such a powerful mix of drugs and receive a diagnosis of bipolar disorder at age 2. (Wen 2007, paras. 9, 14)

Another article quoted Dr Ronald Brown, the head of a committee set up by the American Psychological Association to examine the high rates of antipsychotic medication amongst US children:

> Except for Risperdal, none of the antipsychotics is FDA-approved for children. The overwhelming majority are prescribed "off label." "It is alarming how frequently that is being done," Brown said. "It's of concern that it is being done at all." A child's brain and central nervous system are still developing, so drugs work differently on kids than adults, Brown said. "There are no studies that have shown they (atypicals) are safe, or for that matter, that they are effective for children.” (Farley 2007, paras. 39-41)

4.6.6 **Clinicians media debate ubiquity and meaning of ‘PBD’ symptoms**

A key theme was the non-specific nature of rapid mood shifts and behavioural outbursts in young children. Allied to this was the non-specific nature of symptom reduction simply due to pharmacologic sedation. *The Boston Globe* (Goldberg 2007) quoted a psychiatrist:

> [A] drug may calm down a dangerously out-of-control child and (if) the drug is indicated for bipolar disorder, then it may make sense to diagnose the child with bipolar disorder", said Dr. George Dominiak, medical director of a private psychiatric hospital in Massachusetts. "It's a tail-wagging-the-dog kind of thing … the treatments affect our observations and our labelling as well." (para. 16, 17).

The suggestion that PBD was very much in the eye of the diagnostician was raised by McClellan, quoted in *The Boston Globe* (Allen, 2007):

> Dr. Biederman's staff "can do the same diagnostic interview on 100 children and come up with five or 20 bipolar disorders, and I might do the same thing and find only one or none," said Dr. Jon McClellan. (p. 3, para. 4).

Inadvertently supporting McClellan's suggestion, a feature article in *The New Yorker* titled "What's Normal? The difficulty of diagnosing bipolar disorder in children" reported Papolos as claiming that:

> "[O]nce you see what … [PBD] … looks like, you can't mistake it," he [Papolos] told me. "They call it the View. If you have the View, you get it. It's not apocalyptic, it's a very clear picture." (Groopman 2007)

Pavuluri was quoted in *The New York Times* arguing for the benefits of a single diagnosis for disturbed children (Carey 2007a):

> Pavuluri, director of the pediatric mood disorders program … Chicago, said the label was often better than any of the other diagnoses … "These are kids that have rage, anger, bubbling emotions that are just intolerable for them," Dr. Pavuluri said, "and it is good that this is finally being recognized as part of a single disorder." (para. 14, 15)

Proponents such as Wozniak also emphasised the importance of early intervention, perhaps even at the expense of diagnostic certainty (Goldberg 2007):

> "We support early diagnosis and treatment because the symptoms of this disorder are extremely debilitating and impairing," said Dr. Janet Wozniak, director of the Pediatric Bipolar Program at Mass. General. They "bring reckless and impulsive behaviors here and now and a long-term risk" for suicide, drug abuse, and crime, she said … and "it's incumbent on us as a field to understand more which

> preschoolers need to be identified and treated in an aggressive way ... the overall number of prescriptions is probably small relative to the number of children who need help." (para. 6, 8, 11).

Similar sentiments were echoed by other child psychiatrists in *The New York Times* (Carey 2007b):

> "The first thing to say is that the world does not see the kids we see; these are very difficult patients," said Dr. John T. Walkup, a child and adolescent psychiatrist at John Hopkins University School of Medicine. Dr. Walkup said that when drug treatment was done right, it could turn around the life of a child with a diagnosis of bipolar disorder. (para. 16, 17)

> Dr. Jean Frazier, director of child psychopharmacology at Cambridge Health Alliance and an a/prof at Harvard, said up to three-quarters of children who exhibit bipolar symptoms become suicidal, and that it is important to treat the problem as early as possible. "We're talking about a serious illness with high morbidity, and mortality," Dr. Frazier said, "and for some of these children the medications can be life-giving." (para. 18, 19)

However, in another article in *The New York Times*, Carlson pointed out that learning disorders, ADHD and autism often get obscured by the PBD diagnosis, and emphasised the need for accurate diagnosis:

> According to Carlson, a large group of aggressive and explosive children, who in fact are "diagnostically homeless," are being relabelled as bipolar, which is a development she says is unhelpful both to the children and the field. "Diagnostically it ends up being a very important consideration of what the kid really has," she told me … "If you say, 'Hey, his problem is bipolar disorder,' then you're not going to treat his language disorder, you're not going to give the social-skills treatment he needs," she said. Problematic conditions in a child's home life are also less likely to be addressed if the child's behavioral issues are attributed to bipolar disorder, Carlson said. "Many people, when they hear bipolar disorder, their brain slams shut." (para. 51)

Carlson, via *The New York Times,* had been able to enunciate a clear critique of the primary danger of the PBD hypothesis: the gathering of non-specific childhood emotional and behavioural dysregulation symptoms under what Pavuluri called a single disorder.

Misdiagnosis leads to the wrong treatment, what may be irreversible iatrogenic harm of powerful medications, and failure to address real contributing causes. Investigative journalists were providing the medium for a type of peer review for the PBD hypothesis that had been lacking in the psychiatric literature.

4.6.7 **Split between narrow and broad phenotype proponents**

The differing opinions of the WUSL 'narrow phenotype' PBD researchers versus those of the Harvard-MGH group were also aired publicly and seemed to diverge even more than they had in the academic literature. As reported in *The Boston Globe* (Allen 2007):

> Dr. Barbara Geller of Washington University in St. Louis, adopted a more restrictive view, requiring that children have a series of specific symptoms such as reduced need for sleep before she would diagnose the disorder. But the Mass. General team used broader categories, saying that children who are extremely irritable or aggressive might be bipolar. (p. 3, para. 3)

Geller was more forthright in *The New Yorker* (Groopman 2007):

> "All the medicines that work in bipolar cases also work in kids who are just aggressive," Geller said. "Children with mental retardation who acted aggressively were treated with drugs like lithium, and it helped to mute their behavior. But it also made them very thirsty, so they started drinking from toilet bowls ... The contention that treatment with these drugs 'makes' the diagnosis is frightening – and completely untrue." (p. 32)

Thus Geller, who in the article had defended the ultradian cycling PBD hypothesis, was concerned, like Dominiak, of a "tail wagging the dog" method of diagnosis: that suppressing childhood behaviour with sedatives confirms a bipolar diagnosis.

> Geller went on, "In the clinic, the first question we have learned to ask of parents is 'Have you read the Papoloses' book?' And 'What in the book resembles your child?' And we will get answers like 'My child is irritable and he likes sweets.'" (p. 32)

The Bipolar Child by Demitri and Janice Papolos does in fact list carbohydrate cravings as one of the main signs of PBD (Papolos & Papolos 2002). While a high sugar processed-food diet

may contribute to children's behaviour problems, it is not a recognised criterion for bipolar disorder in the ICD or DSM. *The New Yorker* article reported:

> Papolos, who is not a child psychiatrist, said that he has had children referred to him from all over the country, as many as two a week in the past seven years. He could not immediately recall any child in this group who did not have a bipolar diagnosis, because, he said, "the people who come to see me have read the book." (p. 31)

What is perhaps most concerning about the book *The Bipolar Child: The Definitive and Reassuring Guide to Childhood's Most Misunderstood Disorder* is not that it was a best-seller, nor that the associated website, www.jbrf.org, allowed parents and young people to quickly self-diagnose, but that Dr Papolos' extremely unorthodox version of PBD was not criticised by other PBD researchers or psychiatry in general, until the media furore following Rebecca Riley's tragic death. Papolos belonged to the work group associated with the Kowatch et al. (2005) treatment guidelines in *JAACAP*.

4.6.8 **Neglect of family dynamics, attachment and trauma**

A further aspect of the Riley case was commented on by Newberger (previously cited in 5.5.9.3), regarding the ignoring of psychosocial contextual factors in the Riley case:

> Newberger said it is particularly shocking given that the psychiatrist had to know that the family had a history of domestic violence and other troubles and that the mother's account of a child's behavior in such circumstances cannot be relied upon.
>
> "It's not just a question of dosages; it's a question of the appropriateness of the initial diagnosis and treatment," he said. (Wen 2007, paras. 15-16)

The Boston Globe quoted Harper, a Harvard professor of child and adolescent psychiatry:

> Psychiatrists too often prescribe these medications, which carry side effects such as weight gain and heart disease risk, without addressing problems in the children's lives, said Dr. Gordon Harper, director of child and adolescent services at the state Department of Mental Health. He likened the approach to "tuning the piano while the subway is going by." (Allen 2007, para. 8)

Carlson also continued to be forthright in the public media:

> "Bipolar is absolutely being overdiagnosed in children, and the major downside is that people then think they have a solution and are not amenable to listening to alternatives," which may not include drugs, said Dr. Gabrielle Carlson, a professor of psychiatry and pediatrics at Stony Brook University (Carey 2007b, para. 13)

Professor van der Kolk, an international expert on PTSD, was quoted:

> "Most of the patients I see who have been misdiagnosed have been told they have bipolar disorder," said Dr. Bessel van der Kolk, a professor of psychiatry at a Boston Uni trauma clinic. "The diagnosis is made with no understanding of the context of their life, then they're put on these devastating medications and condemned to a life as a psychiatry patient." (Carey 2007b, para. 22)

The New Yorker article delved further into this:

> April Prewitt, a child psychologist (trained and practising in the Harvard, Boston region) … spends a good deal of time "undiagnosing" children who have been told they are bipolar. In the past three years, Prewitt says, she has seen thirty children and adolescents diagnosed as having bipolar disorder. In her opinion, only two had the malady. "It has become a diagnosis du jour, as A.D.H.D. was five years ago," Prewitt told me … [she] recalled a seven-and-a-half-year-old boy she saw, who lived in an affluent Boston suburb. Max (a pseudonym) had trouble concentrating and was refusing to go to school. His paediatrician had diagnosed bipolar disorder and begun treating him with Risperdal and Seroquel. "It turned out that the diagnosis was 'a divorce situation'," Prewitt said. (Groopman 2007, p. 32).

The article went on to describe Max as medication-free once family mediation therapy was successful.

Californian paediatrician Dr Lawrence Diller criticised the de-contextualised superficial symptom-checklist approach of relying solely upon the DSM criteria, in an opinion editorial (Diller 2007) in *The Boston Globe*:

> While the (DSM) provides helpful clinical guidance in adults, it begins to unravel with its assumptions about discrete and specific disorders in children and ignores the families and environments in which children live. The ultimate absurdity of this

> scientific model is diagnosing bipolar disorder in 2-year-olds and linking it to the adult disorder with the same name - in the process saddling young children as chronic mental patients … (para. 6)

He specifically critiqued Biederman's approach as a form of biomedical reductionism:

> Biederman has produced a number of studies and papers purporting to demonstrate the validity of his diagnosis and treatment. His research has always epitomized the best of what the DSM model of psychiatry could expect. But the diagnoses in the manual, in concept, are closely linked to the medical model of biologically based psychiatric disorders and focus exclusively on the individual. (para. 5)

These clinicians and academics were being quoted as essentially advocating for application of the biopsychosocial model and investigation of the contextual nature of symptom development. In particular it is established science that severe trauma such as childhood maltreatment leads to neurobehavioural responses that lead to affect and behaviour dysregulation which can be mislabelled as bipolar disorder or possibly ADHD or another descriptive diagnosis, if not considered. This has been covered in Chapter 2.5 and is further elaborated upon in Chapter 8 and Part III.

4.6.9 **US managed care system and diagnostic up-coding**

Across 2006 and 2007, comments were made referring to diagnostic up-coding pressures in the US health system. Professor Brown was quoted on this topic in *USA Today,* and while the article predated the Riley controversy, it was related to investigative journalism into the rising rates of atypical antipsychotic prescriptions to children (Elias 2006):

> Insurance coverage rules may encourage the soaring use of antipsychotics for children, as well. "With some companies, the only thing they reimburse for is prescribing. There's little or no therapy," says Ronald Brown, editor of the *Journal of Pediatric Psychology* and a dean at Temple University.
>
> Also, kids with serious mental health problems often have at least one hospitalization, but policies cover only a week or two.

> It can take a couple of weeks just to get medical records and family histories, Penn says, but insurers often extend time if there's a new medicine started, which encourages drug dabbling for children who are not ready to go home. (para. 49)

A paediatric occupational therapist was quoted in a Florida newspaper (*The St Petersburg Times*) lamenting the reimbursement problems after closing his business (Farley 2007):

> “It's difficult to make a living at it,” Leonbruno said. “Insurance companies and Medicaid don't pay enough for therapy, he said. They do, however, pay to reimburse for psychiatric medications.**”** (para. 32, 33)

Brown from the American Psychological Association was again quoted, where he alluded to the political and financial pressures upon the US health system:

> "The bottom line is that the use of psychiatric medications far exceeds the evidence of safety and effectiveness," Brown said. "What people need to do is what's in the best interest of children instead of what's in the best interest of people's pocketbooks. But children don't vote." (para. 17)

The St Petersburg Times reported the financial burden of atypical antipsychotics for childhood diagnoses on the Florida health budget:

> [I]t cost Medicaid nearly $1,800 for each child on atypical antipsychotics. In the last seven years, the cost to taxpayers for atypical antipsychotics prescribed to children in Florida jumped nearly 500 percent, from $4.7-million to $27.5-million. (para. 12)

These media reports were supported by an analysis of physician consultations that involved prescription of antipsychotic drugs to persons aged 20-years and younger across the US (Moreno et al. 2007; Olfson et al. 2006). The study found a six-fold increase in such consultations from 201,000 in 1993 to 1,224,000 in 2002. Between 2000 and 2002 only 36% of such consultations involved provision of psychotherapy “defined as any treatment involving the intentional use of verbal techniques to explore or to alter the patient’s emotional life to effect symptom reduction or behavior change” (p. 680).

4.6.10 **Influence of the pharmaceutical industry**

In a prelude to the Senate Inquiry into conflict of interest relationships that would be launched by Senator Grassley (Chapter 4.7), Diller (2007) linked the PBD researchers with the pervasive influence of the pharmaceutical industry in psychiatry. He noted the reliance of at least some departments of academic psychiatry on industry funding, and how this influences what is highlighted in medical education and conferences:

> [T]here are thousands of potential Rebecca Rileys being treated with multiple psychiatric drugs because Biederman has said it's OK and necessary. Supported by millions of dollars of drug industry promotional funding, Biederman and his colleagues circle the globe offering professional medical "education" for their singular point of view. (para. 7)

Diller linked this industry funding to the politics of medical academia, at least in US child psychiatry, indicating how views and theories favourable to industry may receive preference over theories that are unfavourable:

> Finally, it's sad but true -- the field of child psychiatry is afraid of Biederman. … academic researchers in child psychiatry risk losing their funding if they criticize this darling of the pharmaceutical industry, which provides most of the money these days for psychiatric research. (para. 8)

Carlson was quoted in *The New York Times* regarding the temptation to prescribe medication. Pressure came from the parents of children with emotional and behavioural symptoms, who in a DTCA environment such as the US may believe in a quick medication fix, despite the iatrogenic risks:

> “Parents very often want a quick fix,” Dr. Carlson said, “and doctors rarely have much time to spend with them, and the great appeal of prescribing a medication is that it’s simple … to me one of the miracles of children’s brains is that we don’t see more harm from these treatments.” (Carey 2007b, para. 29)

Several months later she was quoted in the same newspaper more directly attributing the PBD phenomenon to pharmaceutical industry influence:

> We are just inundated with stuff from drug companies, publications, throwaways, that tell us six ways from Sunday that, Oh my God, we're missing bipolar," said Dr. Gabrielle Carlson. (Carey 2007a, para. 29)

Within the US, it was not only advertising to the prescribers, there was advertising to the population at large. A psychotherapist with a media background gave deeper insights in *The New Yorker* article. He described the power of DTCA by the pharmaceutical industry to affect a whole culture:

> Blumberg, who for two years was a vice-president at ABC Motion Pictures, believes that advertising by pharmaceutical companies has influenced the public's view of bipolar disorder … [He] described recent ads, for drugs like Zyprexa, that include a list of symptoms characteristic of the disorder. "But, of course, we all have these symptoms," he said. "Sometimes we're irritable. Sometimes we're excited and elated, and we don't know why. With every form of advertising, the first goal is to make people feel insecure … The advertisements make frenetic, driven parents feel insecure about the behavior of their children" … Parents may fear that children who behave in an eccentric way are at a disadvantage, and in turn pressure the pediatrician or the psychiatrist to come up with a diagnosis and offer a treatment. "Then an industry grows up around it. This, then, enters as truth in the popular imagination." (Groopman 2007, p. 33)

What these clinicians were saying in the media also has academic support. Blumberg is describing what has been termed 'marketing-based medicine' (Spielmans & Parry 2010; Appendices A10, A11) and is explicated further in Chapter 4.21.

4.6.11 **Vigorous defence of Professor Biederman and colleagues**

Despite this very public outcry by academics and clinicians against the validity of the PBD hypothesis, the proponents did not relent. Rather, they mounted an impassioned defence. In the face of what they described as this "firestorm of stinging and misguided criticism" (Rosenbaum & Jellinek, 2007 para. 3) by professional colleagues and journalists in the public media, two colleagues of Biederman responded: both also senior professors in psychiatry at Harvard University, Rosenbaum (Chief Psychiatrist at MGH) and Jellinek (Chief, Child Psychiatry Services at MGH). They co-authored an opinion-editorial in *The Boston Globe* titled

“Heroes in mental health” strongly refuting criticism of professors Biederman, Wozniak and other PBD researchers:

> Four-year-old Rebecca Riley allegedly died of an overdose given to her by her parents, a tragedy that has little to do with any specific disorder. Rather, her death appears to be caused by the parents' misuse of medications. If a child with seizures or asthma were to be given a fatal overdose of medication, would a life-saving therapy and an entire medical discipline be attacked so viciously? It is appalling that Biederman's distinguished lifelong work caring for children has been dragged into this fray. (para. 5)

> Biederman is the most widely cited child psychiatry researcher in the scientific literature. He has moved the field of child psychiatry forward carefully, deliberately. Unlike his critics, his meticulous research has withstood intense peer-review scrutiny, and his work is backed up with rigorous science. (para. 6)

The heads of the psychiatry department of Harvard University gave solid administrative backing to their leading academic professor and his prolific research. In so doing, they implied that all the blame for Rebecca Riley’s death lay with her low socioeconomic status parents, who had marginally increased the nocturnal sedation in a heavy medication cocktail for a pre-schooler. As reported above, the coroner had noted Rebecca’s death had been due to organ damage from "prolonged abuse of these prescription drugs, rather than one incident" (Pringle 2007, para. 29).

These findings by the coroner pointed towards culpability on the part of the prescriber who had trained in the PBD model of early childhood psychiatry within parts of Boston. Nonetheless, Professors Rosenbaum and Jellinek further advocated for their colleague at Harvard. They argued that Biederman’s research and teaching was not related to the clinical case of Rebecca Riley:

> Let’s get the facts right. Joe Biederman had no involvement in the tragic death of Rebecca Riley. He had no knowledge of this child’s diagnosis, no role in developing the treatment alleged to have been administered by the parents. (para. 8)

Yet, as previously mentioned in section 5.5.6, Dr Kifuji’s legal defence stated that Drs Biederman and Wozniak were the ‘leading lights’ in the field who influenced her practice. As

evidenced a number of times in this paper, Professor Biederman had claimed that mania has its onset in the early preschool years, and that adult bipolar disorder pharmacotherapy protocols must be used because parents cannot wait years for research results.

A series of letters in *The Boston Globe* on 24 June 2007 included three from psychiatrists. Irwin, clinical professor of child psychiatry at New York Medical College, cogently describes the "lack of meaningful informed consent" between clinician and a child's guardians "that contributes to the overuse of psychiatric medication in children" (para. 3):

> Parents are frequently not given sufficient information to make the best decision. The benefits of medications are often exaggerated. Parents are rarely informed that certain medications that are effective for adults with a similar condition may not be effective for children or FDA approved for use in children. Risks are similarly minimized. Parents may not be told about serious federally mandated black-box warnings. Alternatives are rarely discussed ...
>
> If we truly empower parents to make informed decisions based on weighing accurate information about benefits, risks and alternatives, children will be protected, psychiatric medication will be used more appropriately, and its overuse will decrease. *Dr Martin Irwin, Manlius, N.Y.* (Irwin 2007, para. 3, 4)

The other two psychiatrists, both from Boston, supported Professor Biederman and the PBD diagnosis. Professor Pies from Tufts university critiqued what he termed ad hominem attacks:

> [There is] … growing evidence from … several countries that young children can also suffer from bipolar disorder. However, the specific age "cutoff," symptom profile, and optimal treatment are matters for continued research, not ad hominem attacks. *Prof Ronald Pies, psychiatry, Tufts University* (Pies 2007)

Doctor Myer who trained at MGH also criticised Dr Diller for singling out Professor Biederman:

> As a child psychiatrist who practices in Massachusetts and who trained at MGH, I am familiar with both academic psychiatry and private practice. Blaming Dr. Biederman for single-handedly turning psychiatry into a pharmaceutical company-driven machine is ridiculous. Dr. Diller, who is not a psychiatrist, is clearly unfamiliar with the current practice of child psychiatry. *Dr M Myer, child psychiatrist in Boston* (Myer 2007)

However, Dr Diller is an experienced behavioural paediatrician who has a prominent media presence and authored several books on the management of emotional and behavioural syndromes, particularly ADHD. His website and publications describe the incorporation of psychotherapy and particularly family therapy in his clinical practice (www.docdiller.com).

Biederman further defended his position in *The Boston Globe* as the debate raged in the wake of Rebecca Riley's death:

> Biederman dismisses most critics, saying that they cannot match his scientific credentials as co-author of 30 scientific papers a year and director of a major research program at the psychiatry department that is top-ranked in the "US News & World Report" ratings.
>
> The critics "are not on the same level. We are not debating as to whether (a critic) likes brownies and I like hot dogs. In medicine and science, not all opinions are created equal," said Biederman. (Allen 2007)

He responded further to his critics in a letter the following year titled "I was doing the right thing", in *The Wall Street Journal* (Biederman 2008), transcribed here in full:

> Your reporting on my relationships with pharmaceutical manufacturers ("J&J Emails Raise Issues of Risperdal Promotion," Marketplace, Nov. 25) didn't tell the whole story. My work on pediatric bipolar disorder focuses on symptoms, impairments and neurobiology - not only on medications. The work of my colleagues and myself has provided a better understanding of this devastating disorder and has led to more effective treatment options. In fact, others have replicated our small studies, leading to FDA approval of certain medications as safe and effective for pediatric use.
>
> The Johnson & Johnson Center, which operated from 2002 to 2005, conducted research on ADHD and bipolar disorder. I called it the J&J Center to be transparent about its funding. The center's goal was to advance science. As a business, J&J naturally sought commercial applications for our work. But any implication that J&J's interests interfered with the center's work is wrong. I never owned J&J stock, and whether the company succeeded financially had no importance to me. (Indeed, I have published research critical of J&J compounds.) What does matter to me is the treatment of children and families experiencing great suffering.

> My outside income mentioned in your article was earned over eight years from many pharmaceutical and nonpharmaceutical sources. In addition, the $58,169 that J&J reported to Sen. Charles Grassley that it paid me in 2001 includes a $50,000 educational and research grant made to Massachusetts General Hospital that wasn't in any way for personal use. In fact, I earned $3,500 from J&J that year, the amount I reported to the senator. (The balance represents reimbursement for legitimate travel expenses).
>
> It greatly concerns me that the Journal has damaged my personal and professional reputation, and profoundly harmed the field of child psychiatry.
>
> Joseph Biederman, M.D.
> Chief
> Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD
> Professor of Psychiatry
> Harvard Medical School
> Boston

The Grassley Inquiry referred to is explored further in the next subchapter. However, arriving late on the scene to the media debate were a highly pro-PBD hypothesis cover story in *Newsweek* magazine and a sceptical documentary on the US *Public Broadcasting Service (PBS)*.

4.6.12 **Max on the cover of *Newsweek***

Despite the Grassley inquiry findings, and diminished credibility of the PBD hypothesis, as late as 2008 the magazine *Newsweek* reported uncritically on a 10-year-old boy in its cover story: “Welcome to Max’s world” (Carmichael 2008; Figure 4.19). Max had been diagnosed bipolar and immediately medicated at age 2-years, 1-month. He had been prescribed a total array of 38 psychotropic medications in his short life so far. This article appeared with much prominence and lack of critical perspective despite the tragic outcome of Rebecca Riley’s case two years earlier.

Removed due to copyright restriction.

Image description: Cover of *Newsweek* with image of young boy and text 'Growing

Up Bipolar'

Image can be viewed at this link: http:// knowledgeisnecessity.blogspot.com/2009/04/growing-up-bipolar-recognition-at-last.html

Figure 4.19: *Newsweek* (26th May, 2008, front cover)

4.6.13 "The Medicated Child"

The US *Public Broadcasting Service (PBS)* in 2008 aired "The Medicated Child" in its investigative series *Frontline* that examined the increasing psychotropic polypharmacy for children. This followed on from a 2001 *Frontline* program that reported on the earlier sharp increase in medications, primarily for ADHD. The 2008 episode focussed on PBD, stating that "now one million children have been diagnosed with a new and controversial diagnosis (PBD)" (*Frontline* 2008).

It was stated that Biederman declined to be interviewed, but Chang, from Stanford University, advocated for early medication of children before PBD could take hold in their lives, justifying this on the basis of the kindling theory that illness course worsens without treatment. "Jessica" and her family and psychiatrist (Axelson from Pittsburgh) were interviewed. At age 12 Jessica had been on multiple psychotropics since age 5 after being diagnosed as manic for stating in an agitated and excited giggling state that she was going to cut her parents' heads off, and this followed a two-week period of being depressed and withdrawn. Old video footage followed of 5-year-old Jessica in her manic state being interviewed by Dr Axelson.

The segment was brief, and Dr Axelson would have, of course, been privy to much more information, but as a child psychiatrist viewing this, I had doubts: although a very early-onset manic episode was a distinct possibility, I would still have considered reactions to stress using various ego-defences as possible explanations of her behaviour, which lacked core signs of mania such as true pressure of speech or thought disorder. It was later mentioned that her father was in the US military and had been deployed to Iraq. There was no exploration in *Frontline* of stressors upon the family when Jessica was age 5.

The *PBS* program presented a wide array of views: if anything, the program leaned towards the sceptical perspective. Professor David Shaffer (Columbia University) was interviewed and a longer transcript of his views than those aired was available on the *PBS* website:

> Out of nowhere bipolar disorder suddenly was being diagnosed left, right and center … The reason why I call it [PBD] fashionable rather than real – fashion I guess implies that it may not be real – is because there are certain bits of evidence that are sorely lacking in that if you do follow-up studies of kids, if you follow back studies of adults who have bipolar illness – clear, conventional bipolar illness – you don't find an awful lot of ADHD in their childhood histories. Equally, if you follow up kids with ADHD, you don't find bipolar as they grow up. So that's a big problem. (*Frontline* 2008)

The episode included interviews with a 4-year-old boy 'DJ', his parents and child psychiatrist, Dr Bacon. Initially prescribed dexmethylphenidate (a stimulant), clonidine and risperidone, DJ's appetite had increased and he was gaining weight. Dr Bacon then added oxcarbamazepine (an anticonvulsant 'mood stabiliser'). The parents viewed the CBS *60 Minutes* program regarding Rebecca Riley with the *PBS* reporter and then decided they wanted to reduce DJ's medication. Despite the parents asking if non-pharmacological therapies are available and if their son can have his medications reduced, Dr Bacon prescribed a fifth additional medication, alprazolam (a benzodiazepine anxiolytic) because his mother reported that DJ has school refusal anxiety. When asked by his mother if therapy could help her son, Dr Bacon replied:

> At this point, I think it's, like, 99 percent medication. Plus, it's harder for him to make use of therapy and to make use of any behavioral program if he's still got a lot of symptoms that he really can't control, even if he tried. (*Frontline* 2008)

The five-drug cocktail prescribed to 4-year-old DJ echoes the regime that Rebecca Riley was taking. "The Medicated Child" screened on Australian *SBS* television. Colleagues and I found it difficult to fathom the biomedical paradigm that Dr Bacon must have been trained in, and the practice standards supported by his peers, that led him to dismiss non-drug interventions for DJ and his parents in favour of simply adding more medication.

Paralleling the decline in PBD in the academic literature from around 2009, the US media appeared to lose interest as news reports became infrequent. However, the media had much to say about conflicts of interest stemming from the Senatorial enquiry led by Senator Charles Grassley (Republican-Iowa).

4.7 The Grassley Commission 2008

4.7.1 The Senator Grassley Inquiry into Medicine-Pharma conflicts of interest

In the wake of the media reports following the Rebecca Riley tragedy and other information about alleged corruption and unethical practices in clinical trials research (Morgensen 2006), US senator Charles Grassley (Republican-Iowa), led an investigation into conflict of interest issues between physicians and the pharmaceutical industry. The Senate Finance Committee, for which Grassley was the chair, focused their investigations on psychiatry and specifically mentioned PBD researchers from MGH-Harvard and the University of Cincinnati, Ohio by name (Grassley 2008). The full statement from the Congressional record of 4 June 2008 is in Appendix D1, excerpts here:

> PAYMENTS TO PHYSICIANS
>
> Mr. GRASSLEY. Mr. President, starting last year, I started looking at the financial relationships between physicians and drug companies. I first began this inquiry by examining payments from Astra Zeneca to Dr. Melissa DelBello, a professor of psychiatry at the University of Cincinnati.

> In 2002, Dr. DelBello published a study that found that Seroquel worked for kids with bipolar disorder. The study was paid for by AstraZeneca, and the following year that company paid Dr. DelBello around $100,000 for speaking fees and honoraria. In 2004, Astra Zeneca paid Dr. DelBello over $80,000.
>
> Today, I would like to talk about three physicians at Harvard Medical School--Drs. Joseph Biederman, Thomas Spencer, and Timothy Wilens. They are some of the top psychiatrists in the country, and their research is some of the most important in the field. They have also taken millions of dollars from the drug companies.
>
> Out of concern about the relationship between this money and their research, I asked Harvard and Mass General Hospital last October to send me the conflict of interest forms that these doctors had submitted to their institutions … Over the last 7 years, it looked like they had taken a couple hundred thousand dollars.
>
> But last March, Harvard and Mass General asked these doctors to take a second look at the money they had received from the drug companies. And this is when things got interesting. Dr. Biederman suddenly admitted to over $1.6 million dollars from the drug companies. And Dr. Spencer also admitted to over $1 million. Meanwhile, Dr. Wilens also reported over $1.6 million in payments from the drug companies.
>
> … That is why Senator Kohl and I introduced the Physician Payments Sunshine Act.
>
> … Before closing, I would like to say that Harvard and Mass General have been extremely cooperative in this investigation, as have Eli Lilly, Astra Zeneca and other companies. I ask unanimous consent that my letters to Harvard, Mass General, and the NIH be printed in the Record.

Senator Grassley later reported that AstraZeneca's payments to Dr DelBello amounted to $238,000 between 2005 and 2007. Grassley's findings were front page news in *The New York Times* when the three MGH-Harvard professors were named (Harris, G and Carey, 2008). The same journalist had previously reported DelBello as having "consulted for 7 other drug makers" aside from AstraZeneca in an article describing the new law mandating publication of pharmaceutical industry payments to physicians (Harris, G 2007)

Following a three-year long investigation, Biederman, Spencer and Wilens were censured by Harvard and required to refrain from all paid industry-sponsored activities for one year and seek approval for such activities for a further two years. The psychiatrists wrote a joint letter to colleagues where they acknowledged they had made "honest mistakes" and may "suffer a delay of consideration for promotion and advancement" (Owens & Sarchet 2011) (see URL: http://blogs.nature.com/news/2011/07/harvard_scientists_disciplined.html).

However, the discrepancies in disclosure of pharmaceutical company sponsorship and income by Professors Biederman, Spencer and Wilens and the sums reported by the companies to Senator Grassley's inquiry – as tabled in the congressional record (Appendix D1) were certainly substantial.

As reported in *The Boston Globe* (Kowalczyk 2011) academics were divided about the effects of the Harvard censure:

> "[T]his all sounds like a little slap on the wrist,'' said Dr. Jerome Kassirer, a Tufts University School of Medicine professor and outspoken critic of close ties between the drug industry and physicians. He pointed out that Biederman is a full professor at Harvard Medical School, so it's unclear how a delay in promotion or advancement would affect him. (para. 10)
>
> But Dr. Benjamin Liptzin, chairman of psychiatry at Baystate Medical Center in Springfield, said he believes the actions "send a serious message that the hospital and medical school take this seriously.'' (para. 12)

Professor Daniel Carlat (Tufts Medical School), who had set up his own psychiatry journal to avoid industry sponsorship, suggested the professional discourse around sponsored research had changed:

> "it was almost expected that if you were an academic that you were working with industry … if you were at a very high level institution like Harvard, there was almost a sense that you were entitled to receive a lot of perks and money for various activities from industry,'' he said.

> "When I get on the phone now and talk to a colleague about a study that just came out, there is much more talk about, 'Was this industry funded, and can we trust the study?' '' (Kowalczyk 2011)

As Carlat is quoted, the Senate Finance Committee inquiry and surrounding media raised awareness within psychiatry of the conflict of interest issues between the profession and the pharmaceutical industry. This was reflected in medical and psychiatric journals and specialty college guidelines on the place of pharmaceutical company sponsorship in CME and research.

4.7.2 **The Physician Payments Sunshine Act**

A positive outcome of the Grassley Inquiry was the drafting and passing of a new law, the Physician Payments Sunshine Act (PPSA), also known as 'section 6002 of the Affordable Care Act' of 2010. Senator Charles Grassley and Senator Herb Kohl were the driving force behind this act of the US Congress, and used the findings of his Senate Finance Committee inquiry to argue the need for such a new law. The law required manufacturers of medications, surgical devices and other health products to disclose payments to physicians or investments by physicians in such products. The data is annually collated to a publicly available website and has been published since September 2014 so it is possible for health employers, researchers and patients to view possible conflicts of interest of clinicians and researchers (Richardson, 2014).

The database is now administered by the Centers for Medicare & Medicaid Services (CMS) as the "'Open Payments' national disclosure program" ((CMS), 2020), and starting from 2021 will be expanded to include some allied health practitioners (Dunphy & Yount, 2019). The database is accessible at URL: https://openpaymentsdata.cms.gov/search/physicians/by-name-and-location . There are calls to internationalise the US 'Open Payments', an article titled "Improving researchers' conflict of interest declarations" in the *BMJ* (Grundy, Dunn & Bero, 2020) argues:

> The Open Payments database, created through the US Physicians Payments Sunshine Act, is a notable model in achieving transparency ... The success of the Open Payments database argues for other countries to establish their own open

> payment databases and for any registry to be publicly funded and coupled with enforcement mechanisms. (p. 5)

4.7.3 Extraordinary *American J Psychiatry* editorial board editorial

A further consequence of Senator Grassley's inquiry was the medical profession, particularly psychiatry in the US, acknowledging the conflict of interest problem and the public and media scrutiny. As a prime example of this shift in awareness, an extraordinary editorial in the *American Journal of Psychiatry* in March 2009 (Freedman et al. 2009) was signed by 24 members of the journal's editorial board as well as the Medical Director of the APA and the vice-chairperson of the APA Steering Committee on Practice Guidelines. The tone was salutary, as indicated by this excerpt:

> Congressional hearings and articles in the *New York Times* or *Boston Globe* are far removed from our own practices. But our profession suffers from these episodes and, more important, our patients do as well, because the public and private resources available for the care of our patients depend upon the public perception of the integrity of our profession as a whole. Therefore, each of us has a personal stake and a professional role in the conflict of interest issue. Most of us may never receive a check from a pharmaceutical company. However, by allowing companies to pay for and thus dictate our CME, we support the marketing context in which these acts occur. Our ethical principles as physicians are designed to protect our patients in many ways — *primum non nocere,* confidentiality, prohibitions of boundary violations. We now need to protect our patients from conflicts of interest in the selection of their treatment. (p. 274)

Bearing such ethical principles from the *Journal of American Psychiatry* in mind, the rest of Chapter 4 will concern the debate surrounding PBD in the psychiatric literature and at conferences.

4.8 PBD in the academic literature and at conferences

4.8.1 Introduction

This subchapter is extensive and follows a chronological narrative of key articles and debates concerning PBD in the psychiatric literature and at conferences. The debate evolved over

time, generally moving from a dominance of the pro-PBD perspective to a return of the classical perspective on bipolar disorder.

Key themes included: the boundaries of bipolar disorder and flexibility of DSM criteria; the biomedical reductionist versus biopsychosocial paradigms; critiques of symptom checklists and structured clinical interviews particularly solely with parents as missing vital information and the child's voice; concerns over widespread pharmacotherapy and iatrogenic adverse effects; the emergence of the Severe Mood Dysregulation (SMD) then Temper Dysregulation with Dysphoria (TDD) and finally Disruptive Mood Dysregulation Disorder (DMDD) diagnostic category incorporated into DSM-5 to reduce use of PBD as a diagnostic label; stark discrepancies in opinions of clinicians and diagnostic rates of bipolar disorder in children and youth between the US and other nations; spread, such as it was, of the PBD hypothesis to some child psychiatry researchers and clinicians internationally; debate over community epidemiological prevalence data; and data emerging from prospective longitudinal studies of offspring of parents with bipolar disorder. The last theme has provided firm data supporting the classical perspective, although one study using the PBD hypothesis differs markedly from the other five studies.

4.8.2 **Key literature and conference debate on PBD validity**

4.8.2.1 **The epidemic begins but not without dissent: 1997-8**

As already described in Chapter 3, the two seminal PBD hypothesis articles were published in 1994 and 1995. Given the strength of the classical perspective, as indicated by the historical review, it is surprising that the PBD hypothesis took hold in the US psychiatric literature and clinical practice so quickly. For example, in the set of 789 PBD articles (Figure 4.1), 78% had US authors and the top eight publishing journals were all US-based: *JAACAP* (73); *Journal of Affective Disorders* (69); *Bipolar Disorders* (52); *Biological Psychiatry* (37); *Journal of Clinical Psychiatry* (32); *American Journal of Psychiatry* (21); *Child and Adolescent Psychiatric Clinics of North America* (13). There were, nonetheless, some dissenting voices.

4.8.2.2 **Klein et al. versus Biederman**

Four years after the publication of the first PBD article, the first sceptical article on PBD appeared, as part of an uncommon 'debate forum' section in *JAACAP* in 1998. The topic was,

"Resolved: Mania is mistaken for ADHD in prepubertal children." Arguing in the affirmative was Joseph Biederman, and in the negative were Rachel Klein, Daniel Pine and Donald Klein (Biederman 1998a, 1998b; Klein, RG, Pine & Klein 1998a, 1998b). This early debate highlighted key controversies about the validity of the PBD hypothesis and is covered here in depth. Biederman's arguments focussed on admission rates in the Boston region for childhood bipolar disorder, symptom phenomenology, familial relationships for ADHD and mania, and the efficacy of treatment with mood stabilisers.

Specifically, he noted that although bipolar disorder was considered rare in children "in our region it accounts for most hospital admissions and emergency calls" (p. 1091). He referred to the earlier research by Carlson and others hypothesising a hyperactive chronic irritable presentation for mania in children and overlap with ADHD. He then referenced his group's research findings, for example, 16% of "262 consecutively referred preadolescent children (<12 years of age)" met "full DSM-III-R criteria for mania" (Wozniak, Biederman, Kiely, et al. 1995). The diagnoses were based upon structured clinical interviews corroborated with the Child Behaviour Checklist (CBCL) (Achenbach, 1991) and Biederman, noting the controversial nature of the diagnosis, stated:

> since the CBCL is an empirically derived instrument, these results indicate that the structured diagnostic interview findings were not due to assessor bias. (p. 1092)

He then referred to his group's familial studies of parents of children with ADHD and PBD, ADHD without comorbid PBD, and normal control children (Wozniak, Biederman, Mundy, et al. 1995). They found ADHD and bipolar disorder both co-segregated in families and that first-degree relatives of children with ADHD plus PBD were more likely to have bipolar disorder than relatives of children with ADHD alone.

Biederman reported "preliminary" findings that PBD children treated in his unit were likely to be prescribed "mood stabilisers" but that "improvement was slow and associated with a substantial risk of relapse" (p. 1092). Nonetheless his group:

> concluded that mood stabilizers were frequently used in manic children and their use was associated with significant improvement of manic symptoms while antidepressant, antipsychotic, and stimulant medications were not. (p. 1092)

This review of pharmacotherapy was published soon after (Biederman et al. 1998). Nine percent (74/792) of consecutive referrals to the MGH-Harvard Pediatric Psychopharmacology Clinic met "DSM-III-R diagnosis of mania" (p. 629). All were called "children" but 39% were adolescents over 12-years-old. Their medication histories and clinical progress were compared over a period varying from six weeks to almost-five years. Only lithium and to a lesser extent carbamazepine were associated with improvement; valproic acid (sodium valproate) was not, neither were the other medications as Biederman had stated in the *JAACAP* debate. This naturalistic open-label pharmacotherapy study revealed most patients were on concurrent medications. Given the age range it may have included adolescents with classical lithium-responsive Bipolar-I disorder, though lithium has evidence of anti-aggression and non-specific sedating properties too (Moncrieff, 1997). The ages of the 37% receiving lithium was not stated.

Despite these shortfalls in methodology, the findings were used to claim that 'children' had mania because of a lithium response. Biederman stated in the *JAACAP* debate that this medication review had been delayed in publication "because of reviewers who question the validity of prepubertal mania" (p. 1098). It is interesting that the article had been submitted in mid-1997, just before the strong push from pharmaceutical companies to rebadge atypical antipsychotics as 'mood stabilisers', and before subsequent studies by Biederman and colleagues to show that atypical antipsychotics functioned as such. In 2001 they concluded that olanzapine's "safety and efficaciousness … made it easy for the patients to be compliant" for twenty-three 5 – 14-year-old (mean age 10) manic subjects (Frazier et al. 2001).

Meanwhile, in the 1998 *JAACAP* debate, Klein RG, Pine and Klein (1998a) argued against the PBD hypothesis, asserting that pre-pubertal emotional dysregulation and disruptive behaviour, inclusive of such behaviours diagnosed as ADHD, were not indicative of mania. Firstly, they argued that the postulated phenomenology of PBD (chronic not episodic and primary irritability instead of expansive mood, with at times irritability) is so markedly different to adult bipolar disorder as to not be the same condition. Secondly, Klein et al. stated that epidemiological studies and the general consensus indicated childhood mania was "very rare" (p. 1094). They quoted the Great Smoky Mountains study (at the time "the most recent epidemiological study") finding of "*not a single child* with mania, and only about 1 per 1,000 children with hypomania among a screened sample of nearly 4,000 children (Costello et al.

1996)". They also questioned the remarkable consistency in diagnosis by the lay interviewers and senior clinicians, that in the seminal Wozniak, Biederman and Kiely et al. (1995) article:

> clinicians concurred in about 99% of cases identified by lay interviewers (sensitivity). Similarly, clinicians agreed with lay interviewers in about 99% of the cases not diagnosed as bipolar disorder (specificity). This remarkable overlap between individuals untrained in child psychiatry and senior child psychiatrists is inconsistent with the observation by the Boston group that "it is very difficult to make bipolar diagnoses in children" (Biederman et al., 1996, p. 1006). (p. 1094)

Further analysing the CBCL findings, Klein and colleagues noted incongruities with mania: the PBD diagnosed children scored highly on anxious, withdrawn, and somatic aches and pains scales, but not in social problems. They queried: "how can these findings be reconciled with the claim that mania in these children is identical with DSM-IV mania?" (p. 1094).

They criticized the MGH-Harvard group's familial studies, saying rates cited of bipolar disorder in relatives of normal control children of 3% (Biederman et al. 1996), and 7% (Faraone, Biederman, Mennin, et al. 1997), "far exceed rates reported in numerous studies and they indicate a substantial lack of specificity for such bipolar disorder diagnoses" (p. 1094). Also, rates of bipolar disorder in adult relatives of the PBD plus ADHD children, although higher than for adult relatives of ADHD alone children, were not higher than adult relatives of normal children. They reported that bipolar offspring studies at that time (Carlson & Weintraub 1993) found "no excess of bipolar disorder or ADHD" (p. 1095). They suggested that the Boston group acknowledge a limitation of "shared diagnostic biases" and quoted from Wozniak, Biederman, Mundy et al. (1995):

> it is conceivable that the increased rate of BPD+ADHD observed among relatives of BPD+ADHD is due to a consistent diagnostic error that affects both probands and relatives" (p. 1095).

Thus Klein RG, Pine and Klein (1998a) argued that "familial validation has not been established" by the "Boston group" (p. 1095).

Klein RG, Pine and Klein (1998a) also highlighted the Boston group's findings (Biederman et al. 1996) that 2% of normal children and 12% of ADHD children developed PBD in a 4-year

period exceeded adult rates of bipolar disorder. They remarked this was highly unusual, given that at the time "no (other) longitudinal study of ADHD children spanning from one to two decades has identified a single instance of bipolar disorder" (p. 1095) and pointed out that the Boston group's high outpatient rates, for example, 17% (Faraone, Biederman, Wozniak, et al. 1997) and 16% (Wozniak, Biederman, Kiely, et al. 1995) far exceeded rates of bipolar disorder in adult psychiatric outpatient clinics.

They criticized the lack of specific symptoms of mania (beyond ADHD, CD and explosive behaviour symptoms) in the checklist-oriented PBD research, that contextual factors had not been considered, and that "there is no substitute for expert, direct clinical assessments" (p. 1095). They concluded that "in sum, the proposed evidence for validity of childhood mania in ADHD is lacking. Clinical, genetic, longitudinal and therapeutic data all fail to document that bipolar disorder masquerades as ADHD" (p. 1095).

Biederman (1998b) rebutted, noting that DSM-IV allows for chronicity in bipolar disorder. He then quoted the first *JAACAP* 10-year review paper of Geller and Luby (1997):

> prepubertal-onset bipolar disorder is a non-episodic, chronic, rapid-cycling, mixed manic state that may be comorbid with ADHD … and CD or have features of ADHD and/or CD as initial manifestations (p. 1096).

Biederman suggested the DSM-IV should be revised to reflect this phenomenology. He criticized the Great Smoky Mountains epidemiological study for repeating the mistake of mistaking PBD for ADHD, and the limitations of assessing 3-month prevalence amongst school-attending children, as PBD children may be absent. He listed a small number of studies that showed adolescents with bipolar disorder have anxiety disorders, bipolar parent offspring studies find higher rates of ADHD and anxiety disorder in children, and disputed Klein et al.'s interpretation of his group's family studies. He conceded the weak treatment data but quoted a contemporary study (Strober et al. 1998) that reported a history of childhood ADHD predicts poorer treatment response to lithium in adolescents with bipolar disorder. Biederman referred to the "kindling" hypothesis of Post, Rubinow and Ballenger (1986, p. 1097), arguing that under-treatment of childhood mania, due in part to hostile reviewers delaying publication of his group's studies of mood stabilizers, was:

> [T]he quiet tragedy of childhood mania: Many psychiatrists face children with ADHD who have horrifying life-long histories of irritable and aggressive mood but have no access to relevant research because reviewers dispute the existence of childhood mania. (p. 1098)

Klein RG, Pine and Klein (1998b) rebutted. They listed studies showing adolescent mania was consistent with classical adult mania apart from more mixed episodes and less psychotic symptoms. Further, they commented that the "debate is not about bipolar disorder in adolescents, but in *prepubertal children"* (p.1099, italics in original), who as yet did not exhibit mania as classically defined. Referring to Biederman's data on mood-stabilizers as "intriguing, but insufficiently documented to provide supportive evidence" (p. 1099), they noted that the lack of response to antipsychotics which generally are effective in mania was surprising. They concluded:

> Most important, we take strong exception to the statement that the children labelled as having bipolar disorder 'met full *DSM-III-R* diagnostic criteria for mania,' as stated in Dr. Biederman's statement. The children failed criterion A, which requires a *distinct period* of affective disruption. The most modest goal of medical classification is a common vocabulary. The *DSM-III* introduced clinical inclusion and exclusion criteria that would, for the first time in history, make this minimal standard possible. Unless we adhere to it, there is little hope of meaningful communication and scientific progress. (p. 1099)

Those strong words from Klein RG, Pine and Klein (1998b) were particularly significant at this point, as the *JAACAP* and other journals published increasing numbers of articles by PBD researchers. Klein et al. had argued that PBD phenomenology was atypical from the classical perspective of DSM-defined bipolar disorder, as well as critiquing the Boston (MGH-Harvard) group's methodology. They stressed the numbers of actual pre-pubertal children being diagnosed was the crux of the controversy. At this early stage, the PBD hypothesis was confined to the US and as Klein et al. demonstrated, a strong case against the hypothesis could easily be mounted in the flagship journal of US child psychiatry. Consequently, it is surprising that more debates and articles sceptical of the PBD hypothesis were not published during this early period.

4.8.2.3 **Carlson's critique**

The next significant voice of dissent came from Carlson in New York. Although she had been an early voice calling for consideration of PBD phenotypes (Carlson 1983), by 1998 she was cautioning against over-diagnosis in her article "Mania and ADHD: comorbidity or confusion" (Carlson 1998). Whilst still advocating for the existence of pre-pubertal mania she acknowledged that "there is no consensus on the *frequency* with which it occurs in youth in general, and preadolescents in particular" (p. 177). She critiqued the use of structured clinical interviews (see Chapter 4.8.3.1). This 1998 article of Carlson's in the *Journal of Affective Disorders* was in an entire issue devoted to PBD. It was the only article in the issue that contained any note of caution, whereas the other articles fully embraced the PBD hypothesis and adult bipolar disorder-derived pharmacotherapy algorithms.

4.8.2.4 **Role of NIMH in supporting validity of PBD hypothesis**

Carlson was present two years later at the National Institute for Mental Health (NIMH) for an important gathering focused on PBD. However, any caution expressed seems to have been over-ridden, as the outcome added fuel to the PBD epidemic. The NIMH hosted a 'research roundtable on prepubertal bipolar disorder'. Present at this gathering were prominent PBD researchers such as Biederman, Geller, Birmaher, Chang and Kowatch as well as Carlson and NIMH psychiatrists Hyman, Leibenluft and Nottelman. The conclusions were outlined in a "Special Communications" report in *JAACAP* in 2001. The following abstract of the report would very probably have been read by a large section of US child psychiatrists:

> **Objective:** A research roundtable meeting was convened at the National Institute of Mental Health on April 27, 2000, to discuss the existing controversial areas in the diagnosis of bipolar disorder in prepubertal children. **Method:** Invited clinicians and researchers with expertise on bipolar disorder in children were asked to share and discuss their perspectives on diagnostic issues for bipolar disorder in prepubertal children. **Results:** The group reached agreement that diagnosis of bipolar disorder in prepubertal children is possible with currently available psychiatric assessment instruments. In addition to phenotypes that fit *DSM-IV* criteria for bipolar I and bipolar II, participants agreed on the existence of other phenotypic possibilities that do not meet diagnostic criteria. Bipolar-Not Otherwise Specified (NOS) was recommended as a "working diagnosis" for the

> non–*DSM-IV* phenotype. **Conclusions:** Bipolar disorder exists and can be diagnosed in prepubertal children. In children who present with both the *DSM-IV* and non–*DSM-IV* phenotypes (i.e., those given a diagnosis of bipolar-NOS), assessment should include careful evaluation of all behaviors that are impairing. Moreover, these children should be monitored systematically to explore stability and change over time in diagnosis and impairment. (p. 871)

Thus, the argument confirmed here is that the NIMH gave its imprimatur, at least in principle, to the PBD hypothesis, and particularly in pre-pubertal children. The text of the article even considered the narrow PBD phenotype described by Geller et al. from Washington University in St Louis as equating to Bipolar-I and Bipolar-II disorder, not Bipolar-NOS:

> Investigators studying BP-I and BP-II phenotypes that fit *DSM-IV* criteria in prepubertal children noted that the most frequent course is a long-duration episode with rapid cycling (ultradian or continuous cycling as the predominant type) and mixed mania (i.e., co-occurring mania and depression) (e.g., Geller et al., 2000a, 2001a). The children who meet *DSM-IV* criteria, are similar to the <20% of adults who have continuous psychopathology with few well periods. (Geller et al., 2000a, b, 2001a). (p. 871)

Further, the broad PBD phenotype described by Biederman and colleagues from Boston was placed in the Bipolar-NOS category: "Investigators studying the BP-NOS phenotypes have also reported chronic, continuous pathology" (Biederman et al., 2000a, b). (pp. 871-872)

While the roundtable did not explicitly use the terms 'narrow' and 'broad', the acceptance of the overall notion of PBD phenotypes by NIMH would have been extremely influential in furthering the national spread of the PBD epidemic.

4.8.2.5 **Glovinsky's historical review**

As previously described (Chapter 2.3), Glovinsky's revisionist historical literature review through to 1980 of bipolar disorder in children and adolescents was published in 2002. This was amid an ascendance in US academia of the PBD hypothesis, and the review perhaps made it easier to dismiss the classical position of pre-pubertal cases being exceedingly rare.

4.8.2.6 *JAACAP* second '10-year review'

The first 10-year review in *JAACAP* (Geller & Luby 1997) had heavily cited the research of the WUSL and MGH-Harvard groups. By the mid-2000s, the PBD hypothesis had been embraced by a number of other academic centres in the US. This was reflected in the text and the 163 references of the 2005 *JAACAP* ten-year review of PBD (Pavuluri, Birmaher & Naylor 2005). The other US PBD research centres that had now come to prominence included:

- Cincinnati Children's Hospital, University of Cincinnati, Ohio (Professor Robert Kowatch, Professor Melissa DelBello)
- The Paediatric Bipolar Consultation Service, University of Pittsburgh, Pennsylvania (Professor Boris Birmaher, Professor David Axelson)
- Paediatric Bipolar Disorders Program, Stanford University School of Medicine, California (Professor Kiki Chang), and
- University of Illinois, Chicago, Illinois (Professor Mani Pavuluri).

This lengthy 26-page review article focussed on "epidemiology, clinical characteristics, assessment, longitudinal course, biological and psychosocial correlates, and treatment and prevention of pediatric bipolar disorder" (p. 846). The review highlighted the NIMH roundtable on pre-pubertal bipolar disorder. It noted that PBD "is increasingly recognized" but that "differing viewpoints on the presentation of bipolar disorder in children are the rule" and that neuroimaging studies showed "frontotemporal and frontostriatal pathology, but none of these findings seemed to be disorder specific" (Abstract, p. 846). It stated that ADHD, schizophrenia and autistic disorders were most likely differential diagnoses, but that co-morbid ADHD, ODD, CD and anxiety disorders were common, as were substance abuse disorders in adolescence. The article had extensive sections on assessment using structured clinical interviews and rating scales such as the K-SADS (Kiddie – Schedule for Affective Disorders and Schizophrenia, Present Episode Version; Puigh-Antich & Chambers, 1978), the WASH-U-K-SADS (Washington University version of the K-SADS; Geller et al., 1996), the YMRS (Young Mania Rating Scale; Young et al., 1978) and CBCL, and particularly pharmacotherapy. Brief mention was made of research suggesting low maternal warmth and family conflict were psychosocial risk factors for PBD, and three family therapy-based interventions devised for PBD were listed for implementation after stabilisation with pharmacotherapy (Fristad, Goldberg-Arnold & Gavazzi 2002). This lengthy review claimed in its conclusion:

> [T]here is consensus on the existence of pediatric BD. There is core agreement on the presence of narrow and broad phenotypes, but additional studies are required to conclude whether the broader phenotypes fall into the bipolar spectrum. High comorbidity with ADHD, disruptive and anxiety disorders, chronicity, recurrence, rapid cycling, mixed episodes, psychosis, suicidality, and risk of substance abuse (in adolescents) characterize pediatric BD. Mood stabilizers and combined SGAs [atypical antipsychotics] and mood stabilizers seem to help, but more short- and long-term randomized, controlled trials are needed. (p. 871)

It is unclear on what basis the authors made their claim that "there is consensus on the existence of pediatric BD", given there was minimal mention of contrarian views and studies. The only reference to the 1998 *JAACAP* 'debate forum' was to cite Biederman (1998a, 1998b) on PBD being predominantly irritable (p. 847) and familial (p. 856), but the views of Klein RG, Pine and Klein (1998a, 1998b) were not cited. The closest reference to the predominant international, non-US perspective in this *JAACAP* 10-year review was the single sentence below, which refers to a comprehensive British review of the controversy (Harrington & Myatt 2003) and a McClellan study of a two-year follow-up of adolescents in Seattle:

> At this time, evidence is not sufficient to indicate that pediatric BD is continuous with adult BD (Harrington and Myatt, 2003), although psychotic adolescent-onset mania appears to be similar to adult BD. (McClellan et al. 1999, p. 853)

However, a closer look at Harrington and Myatt's review of studies reveals that the view in the United Kingdom is that 'classical' adult-like manic states are "extremely unusual before the age of 13" (p. 961). The *JAACAP* review cited a 2-year study of McClellan's yet ignored an earlier 20-year study where McClellan and NZ co-author Werry found only one definite pre-pubertal case of bipolar disorder in paediatric admissions in the capital Auckland (Werry, McClellan & Chard 1991; Chapter 2.4). Both the unbalanced selection of and somewhat misleading reports of international or contrarian perspectives on the PBD hypothesis effectively undermined the *JAACAP* review claim that the validity of PBD was generally accepted.

4.8.2.7 **Kowatch et al.'s treatment guidelines & McClellan's commentary**

A large, and first, 'treatment guidelines' review for PBD was published in *JAACAP* (Kowatch et al. 2005). The guidelines had been developed during a 2-day meeting by 20 clinicians of the

“Child Psychiatric Workgroup on Bipolar Disorder” and members of the CABF. They were sponsored by seven pharmaceutical companies. Both the ‘narrow’ and ‘broad’ PBD phenotypes were accepted and neuroimaging studies were cited as providing evidence of validity. Need for a “comprehensive [diagnostic] assessment” was stressed, but there was no mention of play-based child assessments (p. 218) (see Chapter 4.8.3.4.1). Teacher reports were encouraged but not stipulated, despite the prior critique of Carlson (1998) (Chapter 4.2.1). While the use of structured clinical interviews for diagnosing was extensively covered, there was minimal mention of exploring the background of the child and family in multiple consultation sessions. In terms of treatment the article focussed almost exclusively on pharmacotherapy with seven pages of detailed pharmacotherapy algorithms including two flow-charts, one of which is presented in Figure 4.20 (Kowatch et al. 2005, p. 221).

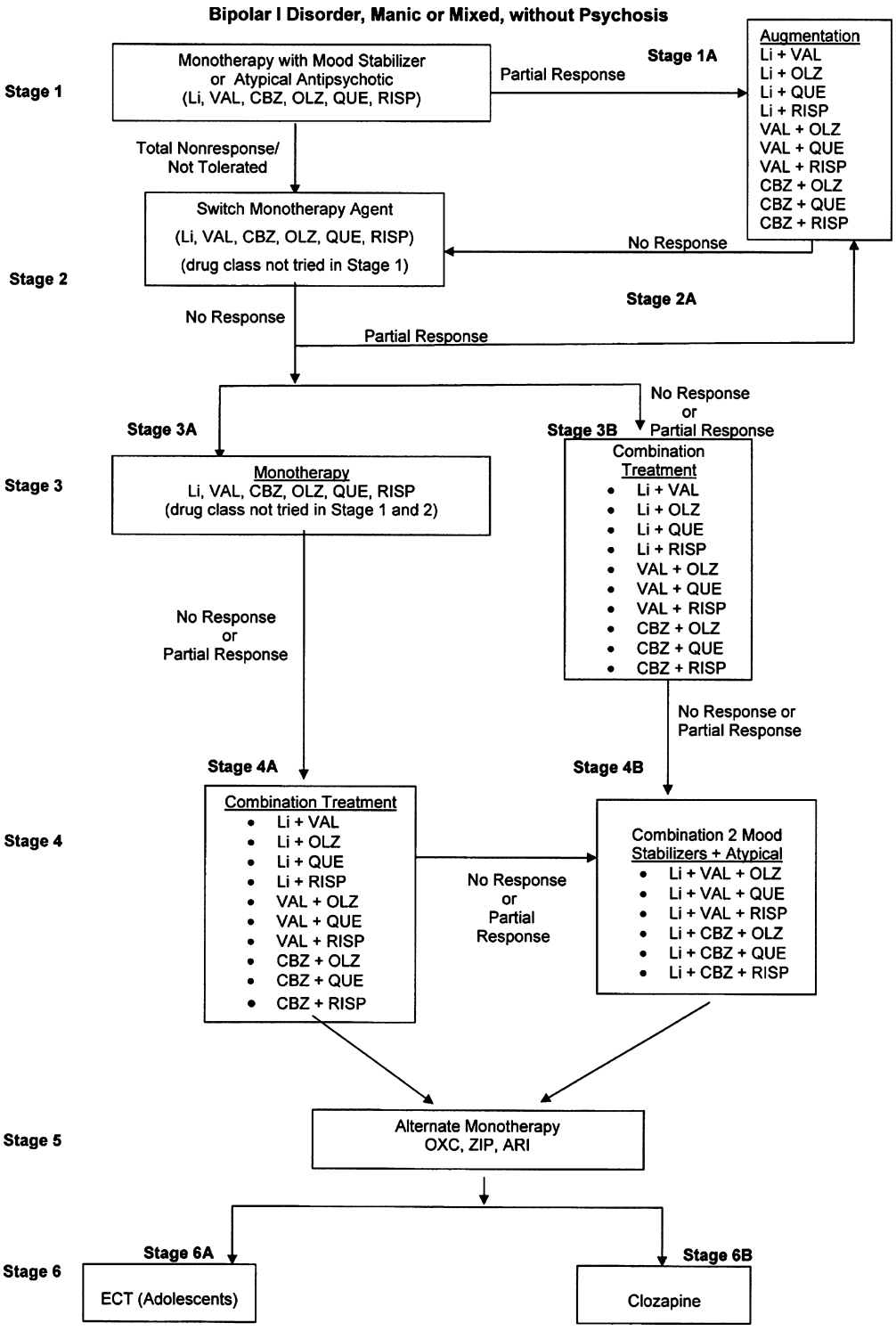

Figure 4.20: Portion of Algorithm I: Bipolar I disorder, manic, acute, without psychosis (Kowatch et al. 2005, p. 221). Reproduced with permission.

Only half a page was devoted to non-pharmacological interventions, primarily detailing a therapeutic alliance with, and providing psychoeducation to, the family and child to ensure

medication compliance. The guidelines did however recommend that medication be limited to children aged 6-years and older.

Accompanying the treatment guidelines was a commentary (McClellan 2005). As this commentary was the first serious critique of the PBD hypothesis to appear in *JAACAP* since the 7-years-previous debate of Biederman v Klein et al. (1998), this serves to indicate how strongly the flagship journal of AACAP supported the PBD hypothesis, especially since *JAACAP* was the leading journal in publishing the large body of PBD literature.

McClellan critiqued the neuroimaging studies as inconclusive and contradictory in their findings. He reiterated the arguments of Klein et al. as to why the validity of PBD was still in question. He went further, however, by outlining the core systemic perspective of child and adolescent psychiatry, pointing out that:

> [T]he developmental and family systemic context of children's moods and behaviour reflect complex problems interwoven with temperament, attachment, parent-child relationships, cognition and other moderating/mediating factors including trauma (p. 237).

He inferred that attention to this critical and sophisticated child psychiatric paradigm was lacking in the PBD research field. McClellan commended Kowatch et al. for at least limiting the recommendations for pharmacotherapy to children aged 6-years and older but lamented: "the rate of psychotropic agents being prescribed to pre-schoolers is skyrocketing" (p. 238). He concluded, as highlighted in the quotation at the beginning of this thesis, that "labelling tantrums as a major mental illness lacks face validity and undermines credibility in our profession" (p. 238).

4.8.2.8 **Further studies 2005**

Nonetheless, in this same year the MGH-Harvard researchers also reported on the previously mentioned (Chapter 3.3.1) trial of two atypical antipsychotics on very young children: a comparison of olanzapine versus risperidone in thirty-one 4 – 6-year-old children with the associated rises in serum prolactin and weight (Biederman, Mick, Hammerness, et al. 2005), as well as an open-label trial of risperidone for thirty 6 – 17-year-old children and youth (mean age 10.1) (Biederman, Mick, Wozniak, et al. 2005), and a chart review of the effects of

aripiprazole for 41 children and youth (mean age 11.5). In the aripiprazole study, it was conceded that results were difficult to interpret due to the multiple other psychotropic medications concurrently prescribed (Biederman, McDonnell, et al. 2005). Despite this, the abstract stated that "aripiprazole may be a useful and well-tolerated treatment" (p.141).

Given that the PBD-labelled children in the MGH-Harvard cohorts were reported as symptomatically very disturbed, the sedative effects of atypical antipsychotics are likely to have diminished such symptoms. Sedating symptoms is not treating an underlying cause or disease process. Wozniak described children with PBD having high rates of comorbid ADHD (73% to 98% in preteens) and other psychiatric disorders: she reported "the age of referral to our clinic is 8 years, about 75% of parents report symptoms beginning during the preschool years" (Wozniak 2005, p. 19). The same group also published a study of a large cohort of PBD children and teens (aged 6-18 years, mean age 10.6) who displayed high comorbidity with anxiety disorders and disruptive behaviour disorders (e.g. ADHD, ODD, CD) (Harpold et al. 2005). Diagnoses were based on the structured parent questionnaire of the epidemiological version of the K-SADS (K-SADS-E; Orvaschel & Puig-Antich 1987). Of 1,650 consecutively referred patients to the MGH, 297 were consequently diagnosed with PBD and 1,385 with one of the disruptive behaviour disorders, 285 were comorbid for both. Therefore 96% of the PBD cases were comorbid for disruptive behaviour disorders. Further, 76% of the PBD group were diagnosed with comorbid anxiety disorders. Harpold et al. (2005) illustrated their findings in two figures, their Figure 1 (p. 21) and Figure 2 (p.22), reproduced here as Figure 4.21 and Figure 4.22.

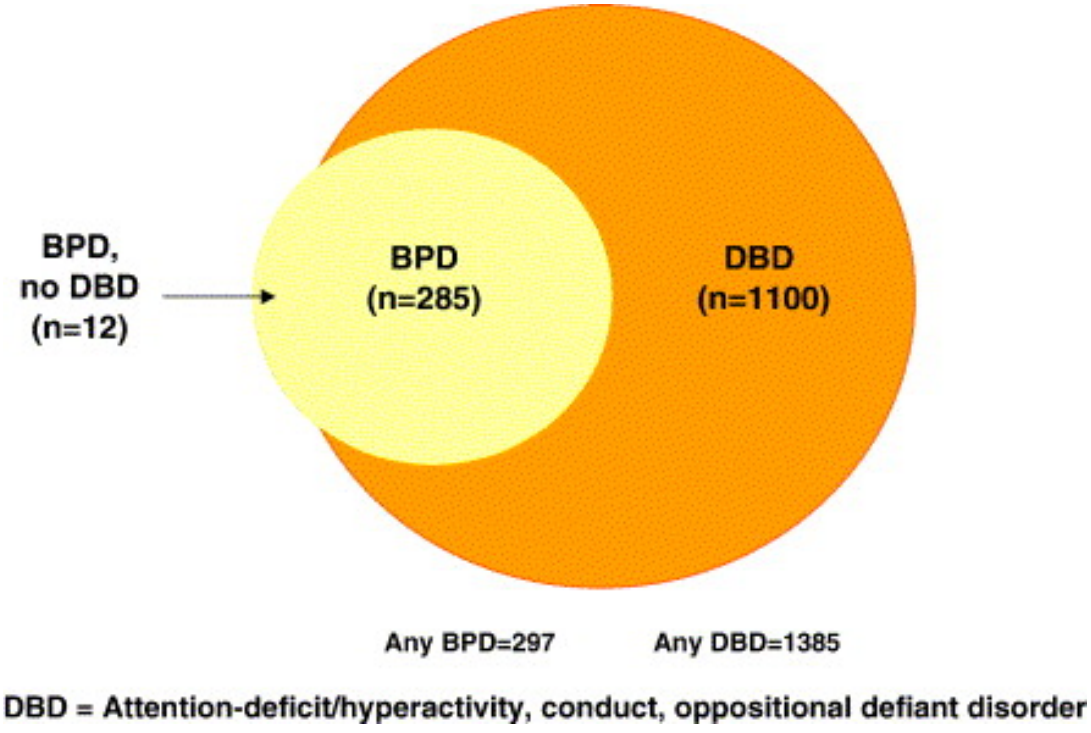

Figure 4.21: Youth with bipolar disorder (BPD) or disruptive behaviour disorders (DBD) (Harpold et al. 2005, p. 21). Reproduced with permission.

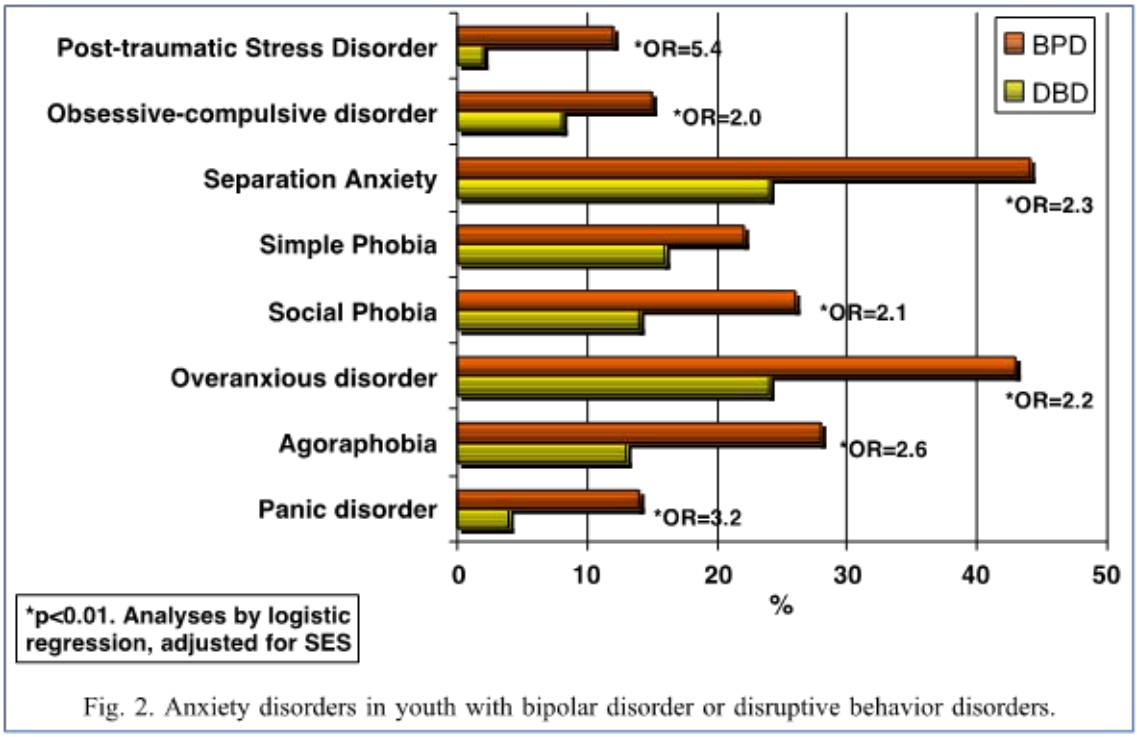

Figure 4.22: Anxiety disorders in youth with bipolar disorder or disruptive behaviour disorders (Harpold et al. 2005, p. 22). Reproduced with permission.

To child psychiatrists trained in the classical biopsychosocial paradigm with emphasis on attachment theory and family systems theory, the results show that the MGH-Harvard group were identifying a group of children with both externalising and internalising symptoms. The logical next step in research would then be an exploration of any attachment insecurity, maltreatment and/or trauma history. As shown in Chapter 8, it appears the MGH-Harvard group are yet to do so.

4.8.2.9 **Harris's critique (2005)**

Published the same year was a critique of PBD by a child psychiatrist who may have seen some of the children from these studies. Her observations confirmed the presence of contextual attachment insecurity and trauma factors (Harris, J 2005). Harris had worked for 3 months on a pre-teen's psychiatric inpatient unit in Boston and the critique was based on her placement. She stated that a quarter of the children aged 3-13 had been diagnosed with PBD and for another quarter their parents were wanting the same diagnosis and medications.

She described two 'PBD' cases, a 10-year-old and an 11-year-old boy: one she re-diagnosed as suffering from PTSD due to severe intra-familial maltreatment, and the other as having autism. Both responded to psychosocial interventions and medication reduction. She described the pressures building within US society for diagnosing children with PBD. Commenting on the 'popularity' of PBD, she wrote:

> Increased diagnosis of bipolar disorder in childhood must be seen in a larger cultural, political, and financial context … Telling parents their child has a biologically based mental illness, although difficult, is far easier than examining family interactions that contribute to behaviour, a task that is sure to invoke parental guilt. Instead of having to deal with problems in the parent-child relationship, parents can see their child as ill … The physician, too, can attain a more positive glow as a fighter for a child who has been misunderstood and labelled as bad but who instead suffers from a chemical imbalance that can be remedied. (p. 531)

She noted that "treatment planning is simplified if the problem is conceptualised as being largely biological, which results in medication" (p. 531) rather than addressing domestic violence and similar problems. Also, she listed diagnostic up-coding pressures as a PBD

diagnosis led to a higher likelihood of financial assistance, health insurance reimbursement and special educational assistance than diagnoses such as disruptive behaviour disorder or PTSD.

In email correspondence with Jennifer Harris on 9 May 2007 she informed me that in her opinion perhaps only one 12-year-old may have had bipolar disorder. She stated:

> Many of the cases … with a label of JBD that I disagree with, tend to have horrendous histories of abuse and neglect, are typically in the foster care system, or in highly disturbed or disrupted families … One recent example was a young child with autism (age 6, if I remember) who was just removed from Mom's care and placed with Dad. Dad worked odd jobs with odd hours and had a different caregiver for him almost every day. In addition, he was in a new classroom, had been put on a huge cocktail of medication to control his behaviour (which not surprisingly got worse) and was actually lithium toxic ... Unfortunately, no-one had thought about what a stress the change in home, inconsistent caregivers, and the disorienting effect of those medications on his sensorium were. The answer to every behavioural change seemed to have been to increase or add meds.

I was later to meet Dr Harris on a visit to Boston; what she described as occurring in the units in her city sounded like a completely different approach to practice to the child and adolescent mental health services I had trained and worked in within Australia and the UK. In contrast to the paradigm that Dr Harris and I shared, the paradigm fostered in parts of Boston seemed to omit the 'psychosocial' from the biopsychosocial model and led to serious iatrogenic harm to children and adolescents.

4.8.2.10 **Special PBD issue of *Biological Psychiatry*, 2006**

In 2006, Professor Biederman authored another editorial in the high-impact-factor journal, *Biological Psychiatry* (Biederman 2006). Titled "The evolving face of pediatric mania", the article commented that "up to 20% of psychiatrically referred children and adolescents satisfy criteria for bipolar spectrum disorders" (p. 901). Biederman again defended the validity of "chronic and continuous … severe irritability as a viable diagnostic feature" that met "unmodified DSM-IV criteria in establishing the diagnosis of mania in pediatric populations" (p. 901). He disagreed with Leibenluft et al.'s (2003; Chapter 3.2.3) effort at defining PBD

phenotypes, which attempted to move chronic irritability away from the bipolar spectrum, and again cited the first *JAACAP* 10-year review as supportive of "childhood-onset mania [being] a 'non-episodic, chronic, rapid-cycling, mixed manic state'" (p. 901).

However, this 2006 issue of *Biological Psychiatry* also contained the first significant article to define Severe Mood Dysregulation (SMD) (Brotman et al. 2006). Brotman's co-authors included Leibenluft of the NIMH, Pine (co-author of Klein) from the 1998 *JAACAP* debate, and Costello, lead investigator in the Great Smoky Mountains study. Revisiting the Great Smoky Mountains study data by adapting criteria from Leibenluft et al. (2003), the authors defined 3.3% of 1,420 subjects aged 9-19 years as having SMD, of whom two-thirds also had a disruptive behaviour disorder diagnosis. In follow-up data in young adulthood this SMD group were at risk of a major depressive disorder (MDD) but not bipolar disorder. The topic of SMD and subsequent iterations of it are discussed in detail in Chapter 4.12.2. In the editorial, Biederman, having to acknowledge the SMD study, concluded on a more impartial note:

> Despite debate and uncertainty, many clinicians recognize that a substantial minority of children suffer from an extraordinarily severe form of psychopathology associated with extreme irritability, violence, and incapacitation that is highly suggestive of mania. Further efforts at clarifying the diagnoses of these very ill children would have substantial clinical and scientific implications. (p. 902)

Biederman's editorial also referred to Dutch research on 10-year-old twins that found the CBCL-JBD phenotype to be familial (Althoff et al. 2006), and research from Chicago investigating neurocognitive correlates of PBD (Pavuluri et al. 2006), that found PBD diagnosed children had attention, working memory and problem-solving deficits with associated academic difficulties.

Robert Post (former Chief, Biological Psychiatry section, NIMH) and Findling and Kowatch published an appeal for greater recognition of pre-pubertal bipolar disorder (Post, Findling & Kowatch, 2006). They critiqued under-treatment of early cases and reported retrospective recall data that found "twenty-six percent of the adult outpatients in the Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) reported that their age of onset of illness was before age 13" (p. 630).

4.8.2.11 **The Pittsburgh COBY longitudinal study**

There were many PBD publications in 2006, but particularly notable was the Pittsburgh group who announced preliminary findings from the multicentre Course and Outcome for Bipolar Youth (COBY) study.

This study has since expanded but in 2006 involved "263 children and adolescents, ages 7-17 years (mean age 13 years), with BP-I (n = 151), BP II (n = 20) and BP-Not Otherwise Specified (BP-NOS; n = 92)" (Birmaher & Axelson 2006, p. 1026). Birmaher and Axelson reviewed the literature and noted that the two studies that had followed up "subsyndromal BP symptoms" (p. 1025), in Oregon (Lewinsohn, Klein & Seeley 1995; Lewinsohn, Klein & Seeley 2000), and Australia (Hazell, P et al. 2003), found that the irritable syndrome did not progress to bipolar disorder in young adulthood. They therefore hypothesised that "the definition of subsyndromal BP used in [these] studies may have been too 'soft,'" particularly if based on irritability (p. 1025). They distanced their research from that of the 'broad' PBD phenotype by deciding to define Bipolar-NOS as:

> [T]he presence of clinical relevant BP symptoms that do not fulfil the *DSM-IV* criteria for BP-I or BP-II and a *minimum* of the following symptoms: (a) elated mood, plus two associated *DSM-IV* symptoms, or irritable mood plus three *DSM-IV* associated symptoms; (b) change in the level of functioning; (c) duration of a minimum of 4 hrs within a 24-hr period; and (d) at least 4 cumulative lifetime days meeting the criteria. (p. 1026)

Thus, while the Pittsburgh group researchers eschew chronic irritability and require mood episodicity, the bar for a Bipolar-NOS diagnosis was set very low: one less symptom is required to qualify as an 'episode' than as stipulated by DSM-IV for an episode of (hypo)mania, and just four 'episodes' lasting a minimum four hours over the course of a child's lifetime would suffice for a diagnosis.

In *Archives of General Psychiatry,* the same year the authors reported age of onset at 8.9(±3.9)-years-old (Birmaher et al., 2006). They described approximately two-thirds had a chronic course, one third achieved euthymia about 80% of the time, and about 40% of those

with Bipolar-NOS convert to Bipolar-II or Bipolar-I. While it is likely that there are cases of classical bipolar disorder emerging in this cohort, the methodology incorporated the brief elevated mood episode of the WUSL 'narrow' PBD phenotype while rejecting the MGH-Harvard 'broad' PBD phenotype. Not surprisingly, the results reported seem in line with those of Geller and colleagues at the WUSL, whom the Pittsburgh group COBY authors favourably cite. They do however use DSM terminology, by using the term 'Bipolar-NOS', whereas the WUSL group called the ultradian cycling cohort 'Bipolar-I' disorder. The DSM-IV provided permissive criteria for the diagnosis of Bipolar-NOS, including:

> [V]ery rapid alternation (over days) between manic symptoms and depressive symptoms that do not meet minimal duration criteria for a Manic Episode or a Major Depressive Episode. (p. 366)

However, it could be argued that the COBY study criteria were even more permissive and did not meet the duration criteria set by DSM-IV, which states symptoms must occur "over days", whereas the COBY criteria like the WUSL criteria required a minimum of just four hours.

Despite these limitations, the COBY study continued to expand. It began in 2000 with a grant from the NIMH and as of 2014 had received approximately $11 million in NIMH funding, by which time the cohort had expanded to a total of 446 subjects (197 children and 249 adolescents). The study is ongoing, although the project end listed on the funding grant website is 30 April 2014 (Birmaher 2014). As such it is an excellent, prospective model, albeit resource intensive, intended to clarify the specific timing and identify the specific syndromes of affect dysregulation that develop into classic Bipolar-I or Bipolar-II disorder. Subjects are interviewed on average every 9 months. Diagnosis of either Bipolar-I, Bipolar-II, or Bipolar-NOS is mainly based on interviews with parents and children/youth with the K-SADS. The question remains, though, if the cases are consistent with classically defined bipolar disorder.

The COBY study findings have led to scepticism from critics of PBD such as Kaplan, who in his *Psychology Today* blog "Your child does NOT have bipolar disorder" noted the COBY results were out of keeping with other research from high-risk offspring studies (Kaplan 2011a). Future results may add clarity: however, the controversy over the boundaries of bipolar disorder does not end once one achieves adulthood as the US also has higher rates of adult bipolar disorder than many other jurisdictions (Paris 2009).

4.8.2.12 **AACAP official guidelines (2007) internal contradictions**

Given the intense media scrutiny to come during 2007 following the death of Rebecca Riley in December the previous year, it was fortunate timing that AACAP published an "official action" "practice parameter" on the subject of bipolar disorder in *JAACAP* in January 2007 (AACAP 2007). According to AACAP's website [https://www.aacap.org/aacap/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx], "AACAP Practice Parameters are clinical practice guidelines developed by the AACAP Committee on Quality Issues to encourage best practices in child mental health." This practice parameter was a more balanced document than the pharmaceutical industry sponsored treatment guidelines (Kowatch et al. 2005) published in *JAACAP* two years earlier. Proponents of PBD whose names appear on the scientific advisory board of the CABF such as Kowatch, Biederman, Findling, Wozniak, DelBello, Axelson, and Youngstrom were still involved, but this time McClellan, who wrote the outspoken commentary to the 2005 treatment guidelines, was included with Kowatch and Findling as one of three chief authors. Carlson and Leibenluft with their more sceptical views particularly towards broad phenotype PBD were also involved; as were "independent experts" Bukstein and Bernet who both served on the AACAP's Workgroup on Quality Issues that oversees practice parameters.

Reflecting this increased diversity of opinion, the new parameter expressed markedly divergent views. It was clear that the AACAP document was far from a consensus guideline. Passages reflecting full validity of PBD were juxtaposed with passages effectively denying its validity. The abstract stated it was yet to be shown that PBD was the same disorder as classical adult bipolar disorder:

> The presentation of bipolar disorder in youth, especially children, is often considered atypical compared with that of the classic adult disorder, which is characterized by distinct phases of mania and depression … Thus, at this time it is not clear whether the atypical forms of juvenile mania and the classic adult form of the disorder represent the same illness. (AACAP 2007, Abstract, p. 107)

The practice parameter at times appeared to accept the validity of PBD:

> Juvenile mania, especially in younger children, often is characterized by symptom presentations and patterns of illness that vary from the classic descriptions of

> bipolar disorder in adults (Bowring and Kovacs, 1992). Changes in mood, energy levels, and behavior are often markedly labile and erratic rather than persistent. Irritability, belligerence, and mixed manic-depressive features are more common than euphoria. High rates of comorbid disruptive disorders are commonly found. (p.111)

The passage went on to describe the narrow and broad PBD phenotypes as outlined by the WUSL and MGH-Harvard research groups. However, a sceptical tone permeated the writing, possibly reflecting McClellan as a lead author. The document noted that both the MGH-Harvard and WUSL research groups found chronicity of symptoms in follow up over several years but stated:

> [T]he debate is whether these problems in youths are best characterized as bipolar disorder and, more important, whether juvenile mania is the same illness as that classically described in adults. (p. 112)

The official recommendations were conservative. Recommendation 2 was that DSM-IV-TR diagnostic criteria be fully followed, including adherence to duration criteria. Recommendation 3 stated:

> Bipolar Disorder NOS should be used to describe youths with manic symptoms lasting hours to less than 4 days or for those with chronic manic-like symptoms representing their baseline level of functioning. (p. 115)

Recommendation 5 seemed designed to reduce diagnoses in preschool age children: "The diagnostic validity of bipolar disorder in young children has yet to be established. Caution must be taken before applying this diagnosis in preschool children" (p. 115). So although the AACAP Practice Parameters affirmed both the ultradian cycling and the chronically irritable PBD phenotypes as Bipolar-NOS, by using the word "youths" and applying this caution to diagnosing "preschool children" it was aiming to reduce the amount of diagnosing of prepubertal children.

In terms of treatment guidelines, the AACAP practice parameter was far more cautious than Kowatch et al. (2005). It noted that evidence for mood stabilizer medication like lithium, valproate and atypical antipsychotic agents was only robust for adolescents diagnosed with classical adult Bipolar-I style mania, and the evidence for pharmacotherapy in Bipolar-NOS (in

other words the PBD phenotypes) and children younger than age 12 was “sparse” (p. 117). The risk of harms was emphasised and Recommendation 8 addressed the need for metabolic monitoring. Recommendation 10 highlighted that: “Psychotherapeutic interventions are an important component of a comprehensive treatment plan for early-onset bipolar disorder” (p. 119) and described preliminary positive outcomes in family therapy, cognitive-behavioural, interpersonal and social rhythm therapies, as well as the importance of thorough liaison with schools and other community services. Thus, the overall emphasis of the parameter stood in stark contrast to the 2005 treatment guidelines with their almost exclusive focus on pharmacotherapy algorithms.

Despite the conservative tone in this ‘official action’ of the AACAP, there seemed to be little change over the subsequent decade in PBD researchers’ published literature and conference presentations, although it is difficult to assess changes in clinical practice in the US. It would still be a few years before more debate over PBD emerged at APA and AACAP conferences (Chapter 4.19.4). However, an anthology with a multifaceted critique of the PBD hypothesis appeared the same year.

4.8.2.13 **An anthology sceptical of PBD: *Bipolar Children***

In contrast to the overall perspective of published literature on PBD in the psychiatric journals, the book, *Bipolar Children: Cutting Edge Controversy, Insights and Research,* was an effort to publish academic critiques of PBD (Olfman 2007). The editor Professor Sharna Olfman (Point Park University) had launched a book series, *Childhood in America,* on similar themes with Praeger Press. In her introduction, she warned of the medicalisation of childhood emotional and behavioural problems, and the prescribing of psychotropics to younger and younger American children.

In email communication with me (S Olfman, 2009, email, 4 June), she stated: “I started my book series because I couldn’t always say what I wanted to in conventional journals.” The book contained an article by Healy and LeNoury (2007; Chapter 4.12) and a range of others, with the chapter titles and authors listed below:

1. Bipolar Children: Cutting-Edge Controversy. *Sharna Olfman*

2. Bipolar Syndrome by Proxy? The Case of Pediatric Bipolar Disorder. *David Healy & Joanna Le Noury*

3. But Don't Call It Science. *Lawrence Diller*

4. Creating the Bipolar Child: How Our Drug-Based Paradigm of Care is Fuelling an Epidemic of Disabling Mental Illness in Children. *Robert Whitaker*

5. The Childhood Bipolar Epidemic: Brat or Bipolar? *Elizabeth J Roberts*

6. Disrupted Care and Disruptive Moods: Pediatric Bipolar Disorder in Foster-Care Children. *Toni Vaughn Heineman*

7. Pediatric Bipolar Disorder and the Destruction of Lived Experience: A Case Study. *William J Purcell*

8. An Invisible Plague: Pediatric Bipolar Disorder and the Chemical Colonization of Childhood. *Daniel Burston*

9. Developmental Neurotoxicity of Industrial Chemicals and Pediatric Bipolar Disorder: A Call to Research. *Philip J Landrigan*

Much well-argued academic discourse was in these chapters, but it was not in the mainstream psychiatric journals. Rather it was in a book that one would need to seek out. As a result, the chapter essays, despite their excellent quality, have few citations. According to Google Scholar (4 February 2018), Olfman's first chapter has been cited 10 times, but the other eight chapters collectively only 12 times. The peer-reviewed academic literature is a foundation of science and the humanities; generally high citations in high-ranked journals should indicate quality research. However, the PBD phenomenon illustrates that with some contentious issues this may not necessarily be so. This may be because some psychiatric journals operate under a biomedical reductionist paradigm, reflecting the influence of pharmaceutical industry revenue to journals (Smith, 2005; Lexchin & Light, 2006; Lundh et al. 2010). This issue is explored in Chapter 9.4.

4.8.2.14 **Healy & LeNoury (2007) critique of PBD as a "created illness"**

The book chapter and journal article of LeNoury and Healy (2007) was a significant and wide-ranging critique of PBD. It had been suggested that simply mentioning PBD even in a critical manner in an editorial in a prominent journal may have the effect of giving it more rather than less credibility as an existing entity (Healy & Le Noury 2007: Healy 2007). This suggestion

was encompassed within a narrative analysis of the PBD phenomenon titled "Pediatric bipolar disorder: An object of study in the creation of an illness" (Healy & Le Noury 2007) in the *International Journal of Risk and Safety in Medicine*.

Healy and LeNoury noted the influence of the pharmaceutical industry in liaison with researchers and self-help organisations like the CABF, direct-to-consumer-advertising (DTCA) of bipolar disorder as a common illness, and these messages reaching desperate parents struggling with children's behavioural problems. Rather than putting brakes on the fad diagnosis, psychiatric academia was fuelling the growing epidemic.

Healy and LeNoury, noting how the PBD diagnosis served many players besides the child, speculated:

> [O]ne has to wonder whether we are not witnessing instead a variation on Munchausen's syndrome, where some significant other wants the individual to be ill and these significant others derive some gain from these proxy illnesses. (p. 219)

Their question was at least partly answered not long afterwards, in the investigations of Senator Grassley's US senate finance committee inquiry that dovetailed with revelations from subpoenaed documents in state and federal litigation against some major pharmaceutical companies. In particular, evidence emerged that such companies desired an increase in bipolar disorder diagnoses to create a market for their on-patent atypical antipsychotic drugs, rebadged as 'mood stabilizers'. As noted in the Introduction, the practice of expanding the diagnostic boundaries of diseases into the less or non-pathological range of symptoms, in order to increase markets for pharmaceutical products, has been termed 'disease mongering' (Moynihan, Heath & Henry 2002). Healy and LeNoury made a case that the PBD epidemic was a manifestation of such disease-mongering.

4.8.2.15 **Geller et al. (2008) *Archives of General Psychiatry***

In the wake of the public scandal following the death of Rebecca Riley, from 2008 there was a slight increase in sceptical articles in the academic literature. Articles aiming to separate 'broad' phenotype PBD away from the bipolar spectrum into the new category of SMD continued to mount (Galanter & Leibenluft 2008; Bradley 2008). However, in concert with

this was a trend towards further conflation of 'narrow' phenotype PBD in the form of the WUSL ultradian cycling hypothesis as equating with DSM-IV Bipolar I disorder.

The highest ranked journal in psychiatry is *Archives of General Psychiatry* and in 2008 its chief-editor declared the most influential and cited article of the year to be: "Child Bipolar I disorder: Prospective continuity with adult Bipolar I disorder, characteristics of second and third episodes; predictors of 8-year outcome" (Geller et al. 2008).

This article was praised in the same issue's guest editorial by Leibenluft titled "Pediatric bipolar disorder comes of age" (Leibenluft 2008). Leibenluft noted the marked "upsurge" in articles on PBD from 1996 and that "consensus has emerged that unequivocal cases of BD occur in pre-pubertal children as well as in adolescents" (p. 1122). She summarised the findings of Geller et al. as follows:

> Extending previous seminal work on pediatric bipolar disorder (BD), Geller et al. [1] present the first longitudinal study following up a large sample of youth diagnosed with pediatric BD into adulthood. Beginning when the subjects had a mean (SD) age of 11.1 (2.6) years, the investigators followed up 115 patients with BD for 8 years, at which time 54 patients were older than 18 years. Of these, 44% had a manic episode after age 18 years, as ascertained by the WASH-U-KSADS, suggesting continuity with previously observed symptoms. (p. 1122)

However, it could be argued, as we did in the following correspondence, that all Geller and her group at WUSL had done was follow their cohort over 8 years and find persistence of ultradian affective lability, with episodes lasting "years" not months, and an almost ubiquitous overlap with disruptive behaviour disorders. The strongest predictive correlation was "low maternal warmth", raising the issue that what was being described as bipolar disorder was possibly the effect of disrupted attachment and family dynamics.

4.8.2.16 **Unpublished correspondence: Parry et al., *Arch Gen Psychiatry***

Colleagues and I submitted a letter to *Archives of General Psychiatry*. Listed here it encapsulates the critique of the proposition that the WUSL PBD hypothesis could be equated with DSM-IV Bipolar-I disorder:

> 10th November 2008.

"Child bipolar-I disorder" is indeed a controversial diagnosis.

Geller et al. (2008) report that 44.4% of a cohort of children and adolescents previously diagnosed with "Child Bipolar I Disorder" had manic episodes after they turned 18. This finding was reported in the medical news ("Bipolar I disorder can begin in childhood, extend into adulthood." (Cassels, 2008)) and general media ("Bipolar disorder in children lingers." (*washingtonpost.com*, 2008)). The reader of these reports and the original paper is likely to conclude that the subjects met ordinary criteria for mania, but such is not the case.

Most children diagnosed with Child Bipolar I Disorder cohort exhibit phenomenology quite different to classically described adolescent to young adulthood-onset bipolar patients. In particular the pattern of "ultradian" cycling of brief mood episodes - Geller et al.'s cohort had a mean of 3.7 such mood swings per day - differs from classical manic or hypomanic episodes. Many would consider euphoric, expansive or elevated mood states used in the diagnosis of Child Bipolar I Disorder as non-specific and open to misinterpretation leading to over-diagnosis, even if they are "inappropriate to context and associated with impairment". Examples given include: *elevated mood: "a happy child laughing in the office in the context of a miserable history (e.g. school suspensions, family fights)"; grandiose delusions: "a manic adolescent, even in the absence of musical talent or ability to carry a tune, might practice all day with the belief he or she can become a rock star"; hypersexuality: "adolescents develop romantic fantasies and delusions about teachers"* (Geller & Luby, 1997).

Geller et al.'s 44.4% who went on to have manic episodes at age 18 and older included 66.7% with ongoing "ultradian" cycling – this group are not necessarily exhibiting classical adult bipolar disorder. Presumably after eight years of participation in the "phenomenology of Pediatric Bipolar Disorders" research program, patients and parents are well trained to detect such symptoms and signs. As well as conferring validity on a contentious diagnosis, we are concerned that Geller et al.'s paper may contribute to the further loosening and expansion of criteria for bipolar disorder amongst adults. Already more than half of bipolar disorder cases in adults may be misdiagnoses (Zimmerman et al., 2008). The British National Institute for Health and Clinical Excellence (NICE) guidelines on bipolar disorder are sceptical of pediatric bipolar disorder and caution against over-

> reliance on the WASH-U-KSADS as used by Geller et al., for making diagnoses in clinical practice (NICE, 2006). Surveys of child and adolescent psychiatrists in Germany (Meyer et al., 2004) and Australia and New Zealand (Parry et al., in press) suggest the majority of clinicians in those countries remain sceptical about bipolar disorder in young children. For such clinicians, the strikingly high correlation of "low maternal warmth" with symptom relapse found in Geller et al.'s cohort suggests alternative diagnostic and therapeutic pathways for equivalent groups of moody children.
>
> We can only concur with the opening sentence from Geller et al. that "Child Bipolar I Disorder is a contentious diagnosis."
>
> Authors:
>
> Dr Peter Parry, MBBS, child & adolescent psychiatrist, senior lecturer, Flinders University, South Australia.
>
> A/Prof Jon Jureidini, MBBS, PhD, child & adolescent psychiatrist, Adelaide University, South Australia.
>
> Dr Gareth Furber, BPsych, PhD, clinical psychologist, Flinders Medical Centre, South Australia
>
> Dr Stephen Allison, MBBS, child & adolescent psychiatrist, senior lecturer, Flinders University, South Australia.
>
> Prof David Healy, MD, psychiatrist, Cardiff University, Wales, UK.

Nonetheless, *Archives of General Psychiatry* chose not to publish these observations, nor any critique of Geller et al. (2008).

4.8.2.17 **Carlson (2009) exploration of childhood 'rages'**

In a further sceptical perspective on PBD, Carlson explored children's explosive behaviour in "Rages – What are They and Who has Them?" (Carlson, Potegal et al. 2009). In this survey of 130 children (mean age 9.7-years) with uncontrollable rages admitted to a pre-teen's inpatient unit:

> [O]ne third of children with rages had been given a bipolar diagnosis prior to admission. However, only 9% of children with rages were given that diagnosis after careful observation. (Abstract, p. 281)

The ages of these children were not stated but four of the eight children had bipolar depression and the other four were diagnosed with Bipolar-NOS on the basis of: "'manic'

symptoms (silly behavior, talking excessively, irritability, and hyperactivity) observed singly at one time or another during hospitalization" (p. 284). Thus, perhaps even these eight cases could need longer term confirmation to be considered as being true bipolar disorder.

Unlike most of the PBD research, this study reported history of trauma and maltreatment: "Fifty-six children (43.0%) were known to have been exposed to significant domestic violence, including physical and/or sexual abuse" (p. 283). Just over half the children settled with the structure of the unit and had no further rages. Children who had further rages in hospital were more likely to have neurodevelopmental delays, ASD and/or ADHD.

Carlson also explored the PBD controversy in *The American Journal of Psychiatry* and the title indicated rising dissention in US psychiatry: "Treating the childhood bipolar controversy: A tale of two children" (Carlson, 2009b). This described two 10-year-old boys in fine detail, one with lithium-responsive bipolar disorder, whereas the other had been misdiagnosed. It critiqued the psychotropic polypharmacy that, particularly in the case of the child without bipolar disorder, caused academic and behavioural deterioration that was mistaken for worsening PBD.

4.8.2.18 **Levin (2009) re-diagnosing and un-medicating disadvantaged youth**

In the United States, sceptical articles like Carlson's were still rare, although anecdotally many US child psychiatrist clinicians were perturbed by use and spread of the diagnosis (E Levin, M Burke, G Elliott, 2009, conversation, May; J Harris, 2007, email 5 September; S Kaplan, S Bair, J Shatkin, 2013, conversation, May). It seemed that US child psychiatrists found it difficult to have 'clinical' articles published, as journals wanted data-based manuscripts. PBD researchers were producing plenty of data with statistics of PBD symptomatology or medication trials. In contrast, it was difficult for critics of the diagnosis to generate data on something they disputed the existence of; appeals to traditional clinical opinion or wisdom no longer carried gravitas.

An example of this occurred when Levin sought to report his 2-year study of children from a 16-bed (two 8-bed units) long-term residential care unit in *JAACAP.* His manuscript was returned within hours of submission for being 'not scientific enough' (E Levin, 2018, personal communication, 28 Feb). His article, with its remarkable results, was subsequently published

in the less conspicuous *Journal of the American Academy of Psychoanalysis and Dynamic Psychiatry* (Levin 2009).

The results included impressive positive changes in key indicators. The children had multiple DSM diagnoses including PBD and were taking extensive psychotropic cocktails. The staff and children were encouraged to reconceptualise the children's problems in terms of the attachment and developmental trauma they had suffered, and staff were then trained in a "complex trauma intervention" model of care involving mentalization strategies. This new model of care led to a 100% reduction in violent incident reports over the 2-year period and an 80% reduction in milligrams of medications prescribed (100% reduction in the 8-bed unit where staff embraced the model fully) (Levin 2009). Case descriptions included a 12-year-old PBD-diagnosed girl whose intellectual disability and 'tongue-tied' speech disorder awaiting surgical correction both resolved when her atypical antipsychotics were withdrawn, eliminating her sedation, extrapyramidal side effects and need for surgery.

The 12-year-old girl was described as 'Maia' in Levin's published article, but in part 4 of an in-depth multi-media investigative journalism report on the issue of psychotropic polypharmacy in California, her story was presented under her real name of Yolanda (De Sa 2014). Levin's initial shock at the residential care units is described:

> The "magnitude and the exaggeration of the dosages" startled him, Levin recalled. … kids were too doped up for him to even assess.
>
> They slept through school on antipsychotics, rocked incessantly back and forth on mood stabilizers, and raced around on too many stimulants. One … "was on so much lithium, he was just shaking like crazy," Levin said. "It was scary."
>
> Levin concluded that the "institutional culture" at Lincoln "favored a quick and easy, and low-cost way of dealing with kids' problems." And the costs were low, he said, because "they were paid for by Medi-Cal, and the agency could always pass the costs of psychotropic medications on to the state."

This insightful series about Californian foster children is available online at: http://extras.mercurynews.com/druggedkids/index.html [Accessed 28 March, 2018]

4.8.2.19 **Carpenter-Song (2009) anthropological perspective**

Carpenter-Song provided an anthropological perspective on the 'medicalisation of children's problems', studying families of various ethnic backgrounds. She stated:

> Whether or not one accepts diagnoses such as ADHD and PBD as legitimate psychodiagnostic entities, it is clear that children's actions and feelings are subject to monitoring through a lens of pathology in ways unique to this historical moment in the United States. (Carpenter-Song 2009, p. 64)

She noted that whereas there had been anthropological/sociological studies on the diagnosis of ADHD, at that time "there exist no anthropological studies pertaining to PBD" (p. 67). Her study of the subjective experiences and views of 20 families found a general difference between Euro-American families' tendency to accept the medicalisation of childhood behaviour and Afro-American families being more sceptical of medicating away anger as yet another racially discriminatory form of social control. This is striking when one considers Blader and Carlson's finding that Afro-American children accounted for most of the steep rise in pre-teen inpatient diagnosis of PBD (Blader & Carlson 2007).

4.8.2.20 **Cicero et al. (2009) less bipolar with advancing age in US**

The increase in bipolar spectrum diagnoses in younger Americans was also brought into question by an article titled "Are there developmentally limited forms of bipolar disorder?" Cicero, Epler and Sher (2009) analysed data from the U.S. National Epidemiological Survey on Alcohol and Related Conditions (NESARC) study between 2001/2 and 2004/5. This data showed that as people grew older, decreasingly fewer individuals reported either a 12-month or lifetime prevalence of bipolar spectrum disorders (Cicero, Epler & Sher 2009; Figure 4.23). This was counter-intuitive if bipolar disorder is a lifelong illness and not over-diagnosed.

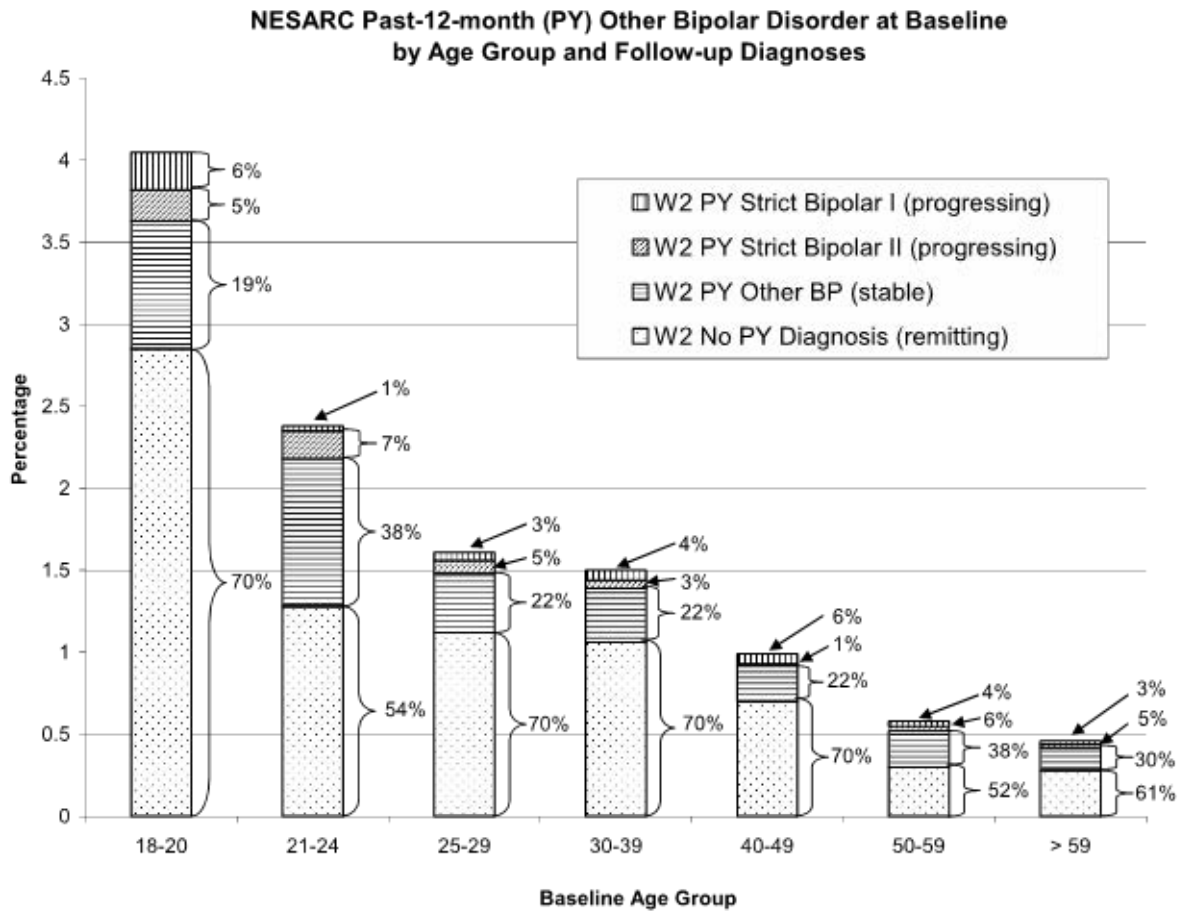

Figure 4.23: Patterns of remission, stability, and progression among participants with past-12-month Other Bipolar disorder using strict National Comorbidity Survey—Replication (Kessler & Merikangas, 2004) criteria in the National Epidemiological Survey of Alcohol and Related Conditions (NESARC; National Institute on Alcohol Abuse and Alcoholism, 2001–2005) baseline sample (including only those who completed the follow- up; *N* = 34,653), presented by age group, with each bar divided by the diagnosis received at follow-up (3 years later). The percentage of each bar accounted for by a specific follow-up diagnosis is provided on the right-hand side of the bar. (Cicero, Epler & Sher 2009, p. 442). Reproduced with permission.

The authors admitted surprise at the downward prevalence with advancing age. They were able to exclude attrition in ageing respondents as a cause. Reviewing the literature on neurodevelopment, they noted that by the mid-20s:

> [N]eurocognitive changes associated with executive functioning and personality changes associated with disinhibition and negative affectivity may help to explain

> a significant portion of the apparent resolution or "spontaneous remission"... (p. 445)

Their main hypothesis therefore was that many cases of bipolar disorder are "developmentally limited forms" (p. 431) that resolve with brain maturation. An alternative hypothesis, that such mood lability before maturity is strictly not bipolar disorder, was not fully explored.

This study has relevance when considering the controversy and debate over epidemiological rates on bipolar disorder in the paediatric age range that is a focus both later in this chapter and particularly in Chapter 6.

4.8.2.21 **The JBRF and Fear of Harm (FOH) phenotype**

Also in 2009 there were further developments from the Juvenile Bipolar Research Foundation (JBRF). The JBRF website http://www.jbrf.org/the-child-bipolar-questionnaire-for-families-use/ (last accessed 26 February 2018) (Chapter 4.3.2) still gave the CBQ online.

The webpage opened with:

> Since 2003, JBRF has collected symptom information from close to 20,000 children diagnosed with, or at risk for bipolar disorder. This enormous database has made possible the line of research that has recently articulated the Fear of Harm (FOH) phenotype … a possible phenotype of bipolar disorder. (para. 2)

A hyperlink followed to a 2009 article on FOH in the *Journal of Affective Disorders* (Papolos et al. 2009). The article would have added scientific veracity to the CBQ for many parents accessing the questionnaire. Papolos et al. published data from over 5,000 children whose parents completed the CBQ. The mean age of onset of:

- first symptoms was 2½-years-old;
- initial diagnosis of PBD was 6-years-old, and
- first psychiatric hospitalisation was 9-years-old.

They claimed the more severe the manic and depressive symptoms, then the higher the FOH score. Given that classical mania is associated with overconfidence, this could be considered as unusual and suggests the CBQ underestimates overconfidence and grandiosity. In fact,

less than 10% (6/65) of items in the CBQ deal with overconfidence or grandiosity (as per pages 64-67 *The Bipolar Child*).

The latter part of the Papolos et al. (2009) article was a review of neuroscience research that, particularly for laypeople, may have been persuasive in indicating that their child was suffering from a brain-based disorder:

> In sum, we suggest that a complex orexigenic neuropeptide circuit first delineated by Emeson and Morabito (2005), that links the hypothalamic nuclei, the median preoptic nucleus (MnPO), ventrolateral preoptic nucleus (VLPO), and the suprachiasmatic nucleus (SCN), as well as the olfactory bulb, amygdala, ventral tegmental nucleus, nucleus accumbens, median and dorsal raphe nuclei, and the locus coeruleus, is primarily responsible for the regulation of the behavioral and proposed physiological features of the FOH phenotype. (p. 36)

Such precise identification of neural structures was perhaps premature. The recent literature (Zilverstand, Parvaz & Goldstein 2017, Pico-Perez et al. 2017) appears mixed as to the extent specific neuroimaging findings can differentiate anxiety and mood disorders. Hypoactive fronto-parietal regions remain the most robust but non-disorder-specific finding, indicating impaired "top-down regulation of negative emotions" (Picó-Pérez et al. 2017, p. 102). However, the role of amygdala hyperactivity is now in question, while hyperactivity in the insula and cerebellar vermis are regions cited for future research.

4.8.2.22 **Neuroimaging presentations at AACAP annual meeting, 2009**

In 2009, I attended two child and adolescent psychiatry conferences: the AACAP annual meeting in Honolulu, Hawaii, US and the FCAP of the RANZCP annual meeting in Queenstown, NZ. While there were 40 oral presentations on the subject of PBD in Hawaii, there were none in NZ.

There were two presentations on the neuroimaging of PBD (Pavuluri 2009; DelBello 2009). The results (hyper-reactive right amygdala hypo-reactive frontal cortex in group diagnosed with PBD) were the same findings as reported in neuroimaging in affect-dysregulated children from maltreatment and attachment trauma backgrounds (Schore 2002). In question time during Pavuluri's presentation I and another member of the audience remarked on this other

body of research and we asked why the children in the study were called “PBD”, could they have not instead been called “affect-dysregulated”. Pavuluri replied that “bipolar is just a man-made label” and it doesn’t really matter what the children are called “but if we don’t call them bipolar, we won’t get funding for our research.” DelBello presented similar findings, contrasting PBD children’s brains with ADHD children without co-morbid PBD. I again remarked on the published neuroimaging findings from the trauma and attachment literature and asked if her research group had examined for maltreatment histories and PTSD. She replied that they had not.

4.8.2.23 **Symposia sceptical of PBD at APA annual meetings, 2009, 2010**

Throughout the late 1990s and early 2000s hundreds of PBD research presentations were given at APA and AACAP conferences, some as industry-sponsored satellite symposia. From discussions with US colleagues at the time, it is noteworthy to mention a symposium at the 2009 APA annual meeting in San Francisco that I participated in with three Californian child psychiatrists was possibly the first overtly sceptical symposium given at an APA or AACAP conference (Parry et al., 2009; Appendix A8). Our symposium was titled: “Pediatric bipolar disorder: A critical look at an American phenomenon.” I presented results of the FCAP of the RANZCP survey on PBD and differences in the Australian and New Zealand versus US health systems; Ed Levin presented his 2 years of work in residential therapeutic units; Mary Burke presented on bioethical issues raised by the PBD phenomenon; Glen Elliott presented what he titled “A dispassionate review of the literature” in which he noted the PBD hypothesis diverged markedly from the classical description.

This time period, perhaps in the wake of the Grassley inquiry, saw more scope for sceptical perspectives at such meetings. The 2010 AACAP meeting included two sceptical symposia on PBD (AACAP 2010a; AACAP 2010b), questioning the PBD hypothesis and highlighting research on contextual factors in affect regulation. This trend at conferences and a decline in PBD articles (Figure 4.1) indicated 2009 to be perhaps the high-water mark for the PBD hypothesis in the US.

4.8.2.24 **Continuing publications on PBD through 2010**

Nonetheless many articles continued to be published. Of particular note were the following: neuroimaging studies e.g. (Pavuluri et al. 2010; Dickstein et al. 2010); pharmacotherapy trials,

for example, a naturalistic study of valproic acid, lithium or atypical antipsychotics in 266 youth (mean age 13.8 years ±2.8) from the University of Pisa group (Masi et al. 2010), an open-label trial of carbamazepine for 27 children (mean age 9.1 years ±1.9) (Joshi et al. 2010) as well as an open-label trial of lamotrigine of thirty-nine 6 – 17-year-olds (mean age 10.8 years ±2.9) by the MGH-Harvard group (Biederman et al. 2010); the Pittsburgh group reported on early results from their high-risk offspring study, the Bipolar Offspring Study (BIOS), finding that the pre-school offspring had an eight-fold increase in ADHD accompanied by subthreshold manic and depressive symptoms (Birmaher et al. 2010).

However, apart from the literature, there were further key events and publications.

4.8.2.25 **Hastings Center 2010 workshop on PBD**

As the trial of Rebecca Riley's parents on murder charges concluded in 2010, many concerned individuals were still seeking to understand the broader picture of how such a situation came to be. Specifically, bioethicists Erik Parens and Josephine Johnston hosted and authored a report of an invitees-only two-day workshop at the bioethics institute, The Hastings Centre. The aim was to bring together exponents and critics of PBD to at least map out the controversy. The workshop was "highly interdisciplinary, including child psychiatrists, psychologists, philosophers, sociologists, anthropologists, and others" (Parens & Johnston 2010). The hosts stressed that the aim was *not* to produce a consensus document but to "fairly describe the debates" (p. 2). The lengthy report, "Controversies concerning the diagnosis and treatment of bipolar disorder in children", was published in *Child and Adolescent Psychiatry and Mental Health.* It was mostly critical of PBD as a valid diagnosis.

In its abstract Parens and Johnston's report noted several problems with the diagnosis:

- Loose interpretations of DSM criteria compromise treatment and research
- Lack of attention to family or social context
- Emphasis on pharmacological treatment
- Ignoring of data supporting psychosocial treatment
- Failure of physicians to fulfil ethical obligation to provide informed consent

Further, the report cited data showing that PBD was mainly confined to the US and listed various diagnostic up-coding factors and commented that:

> [Al]though in the US a BP diagnosis can get children the treatment, school accommodations, and insurance reimbursements they desperately need and deserve, if applied too widely it can do more harm than good. (p. 2)

It listed arguments from PBD researchers:

> David Axelson asked, "if it is possible for children to suffer from anxiety, depression and other disorders experienced by adults, why not BP?" (p. 2)

> … Joseph Biederman argued that nothing is "askew." His explanations for the difference in prevalence rates included that Europeans are biased against recognizing psychiatric disorders in children. (p. 5)

It was suggested that the 'narrow' and 'broad' PBD cohorts may not be so different after all:

> Critics of Geller's approach observed that 97.9% of the sample reported in her 1995 paper also exhibited irritable mood and that her later studies also found rampant irritability in her sample [35,43], raising questions about whether Geller et al. and Biederman et al. are really observing different symptoms. (p. 6)

> Biederman, however, argued that in its intensity, frequency, and association with "out-of-control aggressive behavior," the irritability associated with BP is "qualitatively distinct" from the irritability associated with other childhood disorders (such as ADHD or CD). (pp. 6-7)

In contrast, those sceptical expressed their views as follows:

> Rachel Klein argued, as she had in *JAACAP* in 1998, that it is a mistake to interpret chronic irritability as mania [47]. (p. 7)

> Jon McClellan, for example, was critical of what was being counted as grandiosity, noting that "Normal children display numerous behaviors and beliefs that would be considered pathological by adult standards [45]." (p. 6)

> Gabrielle Carlson observed that "euphoria is easy to find if you're hunting for it, and if you infer it from merely being silly" — as one could given some of the language in the 2005 treatment guidelines for BP in JAACAP [46]. (p. 6)

Ellen Leibenluft from the NIMH was present at the workshop and the report suggests her work redefining 'broad phenotype' PBD as SMD was well received. It was noted that 'DSM-V'

would likely accept this new diagnosis under the name Temper Dysregulation Disorder with Dysphoria (TDD). In 2013 DSM-5 in fact did this but under the name DMDD (Chapter 4.8.5).

One workshop participant, Mary Burke, raised the issue of attachment and developmental trauma being overlooked. This was one of the rare references to attachment theory in the PBD literature (see Chapter 8). She commented:

> [S]ome children diagnosed with BP might more helpfully be diagnosed with PTSD or what she calls "parent-child relationship disturbance" (PCRD), which in her clinical experience are often overlooked. (p. 8)

The Hastings Center report criticized the psychotropic polypharmacy for PBD. It quoted extensively from workshop participant Julie Zito's research, particularly amongst US children in foster and residential care. Both Zito and Carlson cited research that traditional mood stabilizers like lithium and divalproex did not beat placebo in studies of PBD "mania", and although suppressing behaviour, atypical antipsychotics have significant adverse effects. Atypical antipsychotic prescribing was four times greater for pre-pubertal Afro-American boys (p. 9).

The emphasis on pharmacotherapy over psychotherapies in US child mental health services was noted: "Child psychologist David Miklowitz quipped, 'We're getting to the point where psychosocial treatment is being called non-pharmacological treatment'" (p. 10). National Alliance on Mental Illness (NAMI) representative Darcy Gruttadaro said "[while] families want more than medication, financial incentives and our stressed health care system favor writing scripts" (p. 11).

The Hastings Center report criticised US child psychiatry training as fostering a biomedical perspective: "Current training practices, as well as reimbursement policies, may leave some child and adolescent psychiatrists unable to deliver the "biopsychosocial" care that so many agree is the gold standard" (p. 12).

Amongst its conclusions the report, presumably with the dissension of the PBD proponent psychiatrists present, stated:

> Based on our reading in the literature and discussion at our 2-day workshop, we (the non-psychiatrist authors) were persuaded that the BP label may fit poorly many of the children who have received it over the last decade. (p. 11)

Parens and Johnston took this conclusion further by entering a debate over PBD in the prestigious *New England Journal of Medicine.*

4.8.2.25.1 Parens, Johnston & Carlson in *The New England Journal of Medicine* 2010

The two bioethicists followed with an opinion article, co-authored with Carlson, in *The New England Journal of Medicine (NEJM)* (Parens, Johnston & Carlson 2010). The article's provocative title was "Pediatric mental health care dysfunction disorder?" It was an indictment of the US health care system that suffered from a paucity of well-trained therapists, insurers' reluctance to cover nonpharmacological treatments, and the time-intensive nature of the treatments (p. 1855). The article argued that TDD was a necessary measure to reduce the PBD epidemic, but unhelpful if it meant continued labelling with a biomedical illness and first-line pharmacotherapy. They traced the origin of the PBD epidemic to:

> In the mid-1990s, a small but influential group of child psychiatrists began to argue that most children with bipolar disorder do not have discrete episodes of mania but instead have chronic and very severe irritable mood as manifested by explosive, aggressive outbursts or rapid cycling between elevated and depressive moods in a single day. (p. 1853)

4.8.2.25.2 Biederman, Wozniak & Faraone response, *NEJM*, 2010

In reply, Biederman, Wozniak and Faraone stated that Parens et al.:

> [M]isleads, misinforms, and is missing relevant facts. The authors imply that the increase in the diagnosis of pediatric bipolar disorder was due to a cabal of child psychiatrists rather than the increase in published, peer reviewed research". (p. 1187)

They stated that "research from multiple sites supports the validity of [PBD]" and that it was wrong to claim there was "sparse" evidence for medicating children, rather nondrug therapies are "adjuncts to medication, not replacements" (p. 1187).

4.8.2.26 **Frances, chair of DSM-IV task force, on PBD "fad" epidemic, 2010**

Nonetheless, around this same time Allen Frances (Emeritus Professor, Duke University) also laid the PBD epidemic at the feet of "thought leading" child psychiatry academics. Formerly chair of the APA's DSM-IV task force, he penned a strongly worded opinion piece, "Psychiatric diagnosis gone wild: The 'epidemic' of childhood bipolar disorder," in his regular column in *Psychiatric Times* (Frances, 2010b).

Frances called PBD a "fad diagnosis". He accepted some "blame" for "two other false 'epidemics' – of attention deficit and autistic disorders" because DSM-IV criteria had been too lax (p. 1). However, he heavily criticized PBD "because clinicians ignored the DSM-IV definition in favour of a new and largely untested idea that bipolar disorder presents very differently in children" and the new idea swept up "kids who previously received other diagnoses (Attention Deficit, Conduct, Oppositional or Anxiety Disorder) or no diagnosis at all ("temperamental" but normal kids)" (p. 1). Frances saw the PBD fad diagnosis epidemic as the end result of interacting factors:

> The prophets were "thought leading" researchers … Then enter the pharmaceutical industry-- not very good at discovering new drugs, but extremely adept at finding new markets for existing ones. The expanded reach of childhood Bipolar Disorder created an inviting target. The bandwagon was further advanced by advocacy groups, the media, the internet, and numerous books aimed at suffering parents. (p. 2)

He noted the problems of "harmful" medications, and stigma from a diagnosis implying a "lifelong illness" "distorting a person's life narrative" and raising problems for future employment and insurance (p. 2). Frances took a less optimistic view than Parens & Johnstone with regard to SMD/TDD coming into the DSM-5:

> Temper Dysregulation is itself too risky to be included in DSM5 because, once in general use, it would undoubtedly be misapplied to many kids with normal temper tantrums … who don't require any diagnosis and should be kept away from potentially harmful medications. (p. 2)

He called on the NIMH to determine best practice guidelines and "re-educate the public and professionals to the risks of this false 'epidemic' and plan the next steps in a badly needed research program" (p. 3).

4.8.2.27 **Further academic debate, 2011**

As can be seen by the Hastings Center workshop and Frances' opinion article, sceptical perspectives on PBD were making headway. This was reflected in further publications. Normand Carrey, editor-in-chief of the *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, wrote a book review of Healy's *Mania: A short history of bipolar disorder* for the *Canadian Medical Association Journal* (Carrey 2011). Reflecting the conflict of interest scandals rocking psychiatry at that time, Carrey opened his review with:

> Psychiatry has a PR problem. It seems that every week or so, an article or a book comes out revealing how yet another top academic has accepted drug company money, creating the impression in the public's mind that all psychiatrists are on the payroll. (p. 590)

He went on to articulate how this related to the PBD hypothesis:

> Manic–depressive illness, Kraepelin's own term and with a very precise meaning, was supplanted with bipolar disorder, a concept that lends itself better to diagnostic elasticity as it can include the mood fluctuations of personality disorders; then it was just a short step away to the bipolar teen, the bipolar child and finally the bipolar toddler. (p. 590)

Carrey noted how Healy provided historical evidence for how the term "mood stabilizer" owed more to pharmaceutical marketing than to medical science, for its origins and popularity. This "branding" puts pressure on "anxious parents and professionals alike" to stabilise the mood lability of children, preferably with the "improved brand" of mood stabilisers, the on-patent atypical antipsychotics (p. 590).

4.8.2.28 **Special issue of *Adolescent Psychiatry*, 2011**

In 2011, for a relaunch of the journal *Adolescent Psychiatry* the editor, Lois Flaherty (Harvard University; Chair, Committee on Adolescent Psychiatry, AACAP) was keen for a sceptical

perspective on PBD and invited Jennifer Harris, as well as Levin and me, to submit articles. Levin and I contributed as above (Chapter 4.2.3).

Harris summarised SMD research showing that 'broad phenotype' PBD does not progress to bipolar disorder (Stringaris et al. 2009). Additionally, she critiqued Geller et al.'s follow-up of ultradian cycling PBD noting "these young people were not turning into adults with features of classic bipolar I disorder" (Harris, J 2011, p. 59).

However, one could become too sceptical. She described a case of a 13-year-old girl diagnosed with PBD two years earlier who developed obesity, polycystic ovarian syndrome and hyperglycaemia on psychotropic medication, whose parents asked for a second opinion. Harris felt the girl had, like most, been misdiagnosed, but on withdrawal of all medication she became manic. The mother had classical Bipolar-I disorder.

Harris also highlighted diagnostic up-coding factors:

> The length of hospital stays in the U.S. has decreased dramatically (Case, 2007), perhaps leading to an over-emphasis on medication and quicker diagnostic assessments. It has also been recently documented that psychiatrists as a whole (again, in the U.S.) have dramatically decreased the amount of psychotherapy that they are doing from 44% of visits involving psychotherapy in 1996-97 to 29% in 2004-2005 … (Moitabai and Olfson, 2008). … the authors comment that it is likely that reimbursement policies favoring psychopharmacology have played a significant role. … One question that might be worth examining is if therapists who do more psychopharmacology are more likely to diagnose children with bipolar disorder. (p.60)

This particular journal issue had articles on borderline personality disorder and the challenges of cultivating self-reflection in adolescents with attachment trauma and the formation of the 'autobiographical self' and long-term therapeutic alliance for positive prognostic outcomes (Flaherty 2011; Barkai & Rappaport 2011). In comparison with *JAACAP, Adolescent Psychiatry* appeared to be operating according to a different paradigm. However, in terms of US clinical practice, Harris's article noted a shift towards the biomedical paradigm in concert with the trend set by *JAACAP*, despite negative publicity around conflict of interest for PBD researchers.

4.8.2.29 **Robbins et al. (2011)**

These conflict of interest issues were comprehensively reviewed in an article titled "Conflicts of interest in research on antipsychotic treatment of pediatric bipolar disorder, temper dysregulation disorder and attenuated psychotic symptoms syndrome: exploring the unholy alliance between big pharma and psychiatry" (Robbins et al. 2011), but published outside the psychiatric mainstream in the *Journal of Psychological Issues in Organizational Culture*. The authors summarised the reification problem of soft syndromes:

> This bracket creep is in part a result of continuing problems with reliability and validity in *DSM* classification (Kirk & Kutchins, 1992). For these reasons, psychiatry is especially obligated to protect consumers from pharmaceutical influence by permitting diagnostic categories in the *DSM* system only when they clearly demonstrate excellent reliability and validity based on real-world, replicated evidence in the field. (p. 44)

They argued that PBD, TDD and psychosis risk disorder should not be in DSM-5.

4.8.2.30 **More cautious tone on PBD appears on *Medscape***

The role of *Medscape* has already been mentioned in promoting the legitimacy of the PBD hypothesis (Chapter 4.3.3). However, by 2011 *Medscape* had begun to acknowledge the debate over the validity of PBD. Correll and Hauser (2011) in a CME exercise noted that the NIMH had stipulated that DSM-IV criteria should be adhered to; that SMD should replace the 'broad' phenotype and Bipolar-NOS be used for episodic elevated or irritable mood states less than 4 days. These suggestions mirrored the much earlier proposals of Leibenluft et al. (2003). Correll and Hauser concluded:

> In summary, despite growing evidence for the validity of pediatric BP disorder, more and longer-term prospective research is needed to … enable diagnostic consensus. (p. 8, para. 2)

4.8.2.31 **Book: *Your Child Does NOT Have Bipolar Disorder***

Professor Stuart Kaplan (Penn State University, Philadelphia)'s book, *Your Child Does NOT Have Bipolar Disorder,* was published in 2011. Later he authored an identically titled blog on the website of *Psychology Today* (Kaplan 2013). Apart from the anthology *Bipolar Children*,

referred to in Chapter 4.8.2.13 above, Kaplan's book appears to be the only other contrarian PBD book on the market, as a perusal of several dozen PBD-related books on Amazon.com on 22 August 2017 would suggest. It was published in the same series, *Childhood in America*, as *Bipolar Children*.

I reviewed Kaplan's book in *Australasian Psychiatry* (Parry 2011; Appendix A17), concluding:

> Kaplan's contrarian perspective would be mainstream in Australasian or European child psychiatry, where pre-pubertal cases of bipolar disorder are still considered extremely rare (Parry et al., 2009). He notes this fact in the chapter on cultural influences. However Australasian parents read US websites and purchase from Amazon.com and paediatricians and other health professionals follow the US literature, thus this scholarly yet fast paced read has a place on antipodean bookshelves too. (p. 447)

Kaplan's book also received a favourable review in the *Journal of the Canadian Academy of Child & Adolescent Psychiatry* (Matheson & Carrey 2012), noting:

> *Your Child Does Not Have Bipolar Disorder* is a well-organized and readable critique of the diagnosis of pediatric bipolar disorder that presents strong evidence that bipolar disorder does not exist in children under the age of 12. (p. 230)

In contrast, the reviewers in *JAACAP* (Williamson & Althoff, 2012a) were critical of Kaplan's sceptical approach to the Pittsburgh COBY study:

> Dr. Kaplan rightly points out that there has been controversy regarding the diagnosis of bipolar illness. What he inexplicably fails to mention, however, is the growing consensus that … there are some children in whom bipolar disorder seems destined to develop, as demonstrated by the Course and Outcome in Bipolar Youth (COBY) study [2], which Kaplan dismisses as self-fulfilling prophecy. (p. 744)

This led to debate in the letters section of *JAACAP* where I (Parry 2012g; Appendix A22) and Levin (Levin 2012) separately commented on Williamson and Althoff's critique. I noted that:

> It is interesting that the book review of Kaplan's *Your Child Does NOT Have Bipolar Disorder* by Williamson and Althoff [1] varies from the favorable book review I

> wrote for *Australasian Psychiatry* [2]. This variation likely reflects the geographic disparity in views on Pediatric Bipolar Disorder (PBD). (p. 1218)

Williamson and Althoff, in their reply to Levin and me, made no reference to this geographic aspect of the diagnosis. They commended Kaplan for addressing the over-diagnosis of PBD. However, they asserted that to describe pre-pubertal cases as extremely rare to non-existent was an extremist position (Williamson & Althoff, 2012b). From a US perspective, Williamson and Althoff's view could seem a moderate consensus position. However, from an international perspective, the rates of pre-pubertal diagnoses in the COBY study seemed anomalously high. Kaplan invited me to post two guest articles on his blog, to cover this geographic diagnostic disparity (Parry 2012b; Parry 2012c) for a US readership.

4.8.2.32 **Conflict of interest and reification of DSM NOS categories**

Melissa Raven (Flinders University) and I used the PBD phenomenon as a case example of "Psychotropic marketing practices and problems: Implications for DSM-5" (Raven & Parry, 2012; Appendix A24). We described the problems associated with the reification of diagnoses, particularly facilitated by DSM NOS categories, and the several proposals for DSM-5 that argued for further loosening of criteria such as for adult ADHD and "attenuated psychosis syndrome" (p. 513). We suggested there is a direct link between the validity of diagnostic constructs, clinical outcomes and possible iatrogenic harm to the patient:

> The over-inclusiveness of the draft DSM-5 criteria, if carried through to the published manual, will undoubtedly be exploited by the pharmaceutical industry, using KOLs, disease awareness campaigns, and other marketing strategies. This will benefit drug company profits, but many patients will be inappropriately diagnosed and treated with potentially harmful drugs. (p. 515)

One way to prevent such an outcome is to consider biopsychosocial contextual factors contributing to emotional and behavioural symptoms. In other words, to avoid what Eisenberg (1986) referred to as 'mindless psychiatry'.

4.8.2.33 **Parry & Levin (2012) PBD in an era of 'mindless' psychiatry**

Levin and I critiqued the PBD hypothesis, setting the diagnosis in its historical-cultural context, in "Pediatric bipolar disorder in an era of 'mindless psychiatry'" in the *Journal of Trauma and*

Dissociation (Parry & Levin 2012; Appendix A18). Like Healy and LeNoury (2007) we argued that PBD was a product of several interactive factors, rather than the discovery of some real disorder. Specifically, we argued that PBD had arisen during a paradigm shift to:

> [A] current era of "mindless psychiatry" that emphasizes neurobiological explanations for emotional and behavioral problems with limited regard for contextual meaning. Associated with this has been a tendency within psychiatry and society to neglect trauma and attachment insecurity as etiological factors; the "atheoretical" (but by default biomedical) premise of the Diagnostic and Statistical Manual of Mental Disorders (3rd and 4th eds.); the influence of the pharmaceutical industry in research, continuing medical education, and direct-to-consumer advertising; and inequality in the U.S. health system that favors "diagnostic upcoding." Harm from overmedicating children is now a cause of public concern. (pp. 51-52)

These factors, reflecting the dominance of 'descriptive psychiatry' in an era of biomedical reductionism, are all expanded upon within this thesis, however, as Jennifer Harris (2012) in the next section indicates, there are also psychodynamic reasons for 'diagnostic upcoding'.

4.8.2.34 ***Carlat Child Psychiatry Report*, 2012**

An invitation onto the editorial board of the *Carlat Child Psychiatry Report* (*CCPR*) made it possible to participate in a special issue on PBD. The readership of the *CCPR* is about 1,000 US child psychiatrists. In this issue I argued that PBD remained primarily a US phenomenon due to diagnostic up-coding factors (Parry 2012d; Appendix A23). Harris (Harris, J 2012) expanded upon psychodynamic factors that drive clinicians to diagnose PBD, her article brought deeper insight into diagnosing practices:

> Our narcissist defences move us towards accepting ideas that make us feel useful and powerful, sometimes without appropriate credulity. … There may be a strong push to label the child because it will alleviate parental guilt by seemingly confirming that there is "something wrong" medically with the child and therefore not the parents' fault. Alternatively, it could mean that the parents do not need to look too closely into their child's suffering because the answer is a medication adjustment, not a deeper emotional one. Sometimes as providers we are pulled into these dynamics unawares … Parents who see their out-of-control children as

> all bad, hostile, or manipulative may move us as providers to give an alternative narrative that is less pejorative to the child. In an effort to protect the child, we may feel drawn to giving a label that implies that the child's behavior is not the child's fault and makes the parent more empathic. Parents more easily understand something that has a clear label and a history behind it, than a discussion of why it's important to be understanding … In the face of societal skepticism and sometimes hostility to mental illness, it is tempting to flee to certainty. It is uncomfortable to say, "I don't know, and I'm not sure how to help." The reality in child psychiatry, however, is often that we don't know. It takes time for illnesses to reveal themselves, and even when they do they often don't fit clear diagnostic boxes. It takes a tremendous amount of resilience and ego to be able to feel comfortable with that, and meet families where they are (which is often confused, upset, guilt-ridden, scared, and sometimes angry). The temptation to offer a diagnosis, and make ourselves feel smart and useful, is very strong and shouldn't be ignored. (p. 9)

Leibenluft outlined the work on SMD as an alternative to 'broad phenotype' PBD (Leibenluft 2012). The *CCPR* issue included articles by pro-PBD researchers on pharmacotherapy (Goldstein 2012) and neuroimaging of the effects of pharmacotherapy (Pavuluri 2012). An interesting point was made with reference to ADHD and PBD by Pavuluri, who stated:

> I want to point out that these are man-made labels. I believe that no matter what the disorder is, the labels are important only insofar as they help us communicate the larger picture (p. 8).

Given the markedly divergent views on what constituted bipolar disorder in the paediatric age range, the accompanying *CCPR* editorial noted the controversy:

> The diagnosis, treatment, and very existence of pediatric bipolar disorder is one of the most contentious debates in our field. … Some of these articles on bipolar disorder may seem to directly contradict each other. Our objective is to provide you with information from many viewpoints and leave the rest up to you. (p. 1)

4.8.2.35 **Carlson & Duffy (2013) *JCACAP***

Carlson co-authored with Professor Anne Duffy (Dalhousie University, University of Calgary), in the *Journal of the Canadian Academy of Child and Adolescent Psychiatry (JCACAP)*, which effectively expressed the classical perspective (Duffy & Carlson 2013). They stated:

> Evidence overwhelmingly suggests that BD typically onsets in adolescence and early adulthood, with the depressive polarity of the illness dominating the early course. Non-specific childhood antecedents have been noted in some high-risk individuals. However, in youth *without* a confirmed familial risk of BD, manic-like symptoms have little prognostic significance for BD and not uncommonly form part of the normative adolescent experience. Over-emphasis of symptoms and reliance on parent report alone, alongside the relative neglect of the child's developmental stage and risk profile, contributes to the over diagnosis in young children and under recognition of BD early in the clinical course. (p. 6)

4.8.2.36 **APA annual meeting, 2013**

At the APA 2013 annual meeting in San Francisco, where the new DSM-5 was launched, three US child psychiatrist colleagues and I presented a symposium critiquing PBD and related aspects of biomedical reductionism in current US child psychiatric practice (Levin et al. 2013). My co-presenters were Ed Levin, Professor Stuart Kaplan (Penn. State University), and Stuart Bair, a senior child psychiatrist in San Francisco with extensive experience across the US from years of locum work. Our symposium was entitled: "Pediatric bipolar disorder in its historical context: An examination of reasons for its controversial status." The individual presentations were:

> Levin: "Developmental trauma disorder is not just for kids: mental and physical consequences of early trauma in a geriatric population." Building on his previous work in the youth residential centre, Levin suggested unaddressed childhood trauma, if misdiagnosed throughout life, reasserts itself late in life.
>
> Bair: "Paradigm shift: the evolution of the concept of depression, related disorders, and the rise of the diagnosis of pediatric bipolar disorder." This was an historical account of how diagnoses come in fashionable waves, in concert with the on-patent class of medication.

> Parry: “PBD or DMDD: but where’s the trauma? Are attachment and trauma considered in pediatric bipolar and disruptive mood dysregulation disorders?” This was a commentary on the striking absence of reference of developmental and attachment trauma in the PBD research that had again been ignored in the DMDD research (Parry, 2013).
>
> Kaplan: “In the mind of the beholder: diagnosing bipolar disorder with structured psychiatric interview.” Here Kaplan examined how the structured clinical interview approach to diagnosis is flawed, he critiqued the COBY study and cited research by Galanter et al. (2012).

Although ‘broad phenotype’ PBD had just been officially re-categorised by DSM-5 (launched at the same APA meeting) as DMDD, Biederman and Wozniak presented a symposium titled: “Advances in pediatric bipolar disorder research.” The objectives were listed in the APA conference guide as:

1. Understand the CBCL and its utility in identifying youth at risk for bipolar disorder.
2. Recognize that pediatric bipolar disorder in youth persists into mid and late adolescent years … with high levels of morbidity and disability.
3. Recognize the association between PTSD and BP-I disorder in youth, which indicates that BP-I disorder is a significant risk factor for PTSD in youth.

This indicated no real shift by the MGH-Harvard group despite the contemporary publication of DSM-5. Their third point alludes to the MGH-Harvard group’s theory (Chapter 8) that young children have primary PBD, and their resultant behaviour disturbs parents and their environments, which leads in turn to secondary traumatic experiences. This reverses the usual approach of identifying trauma as a potential causative factor.

Further critiques of PBD have emerged at recent APA and AACAP meetings, notably by Professor Joel Paris in a paper titled: “Why affective instability is different from bipolarity” in a symposium at the APA’s 165th annual meeting titled: “Controversies in the under versus over diagnosis of bipolar disorder” (Paris 2012; Prologue, p. 22). However, these have, in the main, arrived late in annual discussion venues in American child psychiatry and consequently had less effect than if such sceptical positions and debates had featured earlier.

4.8.2.37 **Carlson & Klein (2014) 'conservative' vs 'liberal' perspectives**

Gabrielle Carlson co-authored a comprehensive review of the PBD hypothesis controversy with her Stony Brook University colleague Daniel Klein (not the Donald Klein of the 1998 *JAACAP* debate). They critiqued the methodology of structured clinical interviews, favourably citing Galanter et al. (2012) (Chapter 4.8.3.4), and also critiqued the methodology of the meta-analysis of community epidemiological studies of Van Meter et al. (2011) that led to an overstatement of the prevalence rate.

The argument within the article was "How to understand divergent views on bipolar disorder in youth" (title, p. 529). Carlson and Klein contrasted the 'liberal' perspective of the adherents to the PBD hypothesis, with the 'conservative' classical perspective of how and when bipolar disorder develops. They noted the 'liberal' pro-PBD hypothesis leads to the diagnosis of many pre-pubertal cases and high rates of comorbid ADHD, whereas the traditional 'conservatively' diagnosed youth closely approximate Bipolar-I disorder in classically diagnosed adults.

There was little help in recourse to either the PBD hypothesis literature or the classical perspective literature of familial co-morbidity, because the findings reflected the underlying assumptions, and methodology was based on how the boundaries of bipolar disorder were conceptualised. Therefore, they concluded:

> Both perspectives can claim evidence for reliability and validity that support their positions. However, the samples are so different that it is difficult to compare studies conducted from these different perspectives (p. 529).

This significant difference in perspective is well illustrated in the international diagnosis rates, particularly as reported since Carlson and Klein's 2014 article. Carlson and Klein's observation that a gulf persists between those adhering to a 'liberal' view of bipolar disorder that allows for belief in the PBD hypothesis, and those adhering to a 'conservative' or classical view that leads to significant scepticism, is where we shall leave this chronological account of the academic debate over PBD. The next subchapters from 4.8.3 to 4.8.8 will examine individual themes in more depth, before we return to summarising the most recent developments in the academic debate in Chapter 4.8.9.

4.8.3 **Critique of symptom checklist diagnosis approach**

As described in Chapter 3 and in the literature review in this chapter, symptom checklists in the form of structured clinical interviews were the mainstay of diagnosing PBD in research settings. They were also replicated in questionnaires to the public on websites such as that of the Juvenile Bipolar Research Foundation's website and in the book, *The Bipolar Child,* with the Child Bipolar Questionnaire (CBQ). Criticism of these checklists included that they relied on a descriptive psychiatric paradigm that neglected contextual factors and the meaning of emotional and behavioural responses to such contexts.

4.8.3.1 **Carlson (1998)'s critique of structured clinical interviews**

In her article "Mania and ADHD: comorbidity or confusion" (Carlson 1998) she critiqued the use of structured clinical interviews in diagnosing PBD, observing that "most structured interviews were never designed with children in mind and have been `back adapted' for use" (p. 178). She gave the example of how sexual behaviour in children could either be the acting out of sexual abuse trauma or even simple childhood exploration of sexuality, but easily misinterpreted as manic hypersexuality on rating scales. She noted the K-SADS was based on the adult version of this instrument and failed to adequately examine for "oppositional defiance or incipient conduct disorder", and that the Young Mania Rating Scale (YMRS), as devised for adult mania (Young et al. 1978) but widely used in PBD was:

> designed for quantifying (not diagnosing) an episode of mania. There was no consideration in its design to come up with ways of discriminating either ADHD or children with temper tantrums/intermittent explosive disorder or language disorders. (p. 179)

She commented that the complexity and contextual nature of childhood psychopathology meant that "a structured interview, even if it takes a day and is done by careful interviewers, may not replace longitudinal assessment with multiple informants" (p. 179).

On this note she disclosed that:

> every time I prematurely conclude from the parent history that I know what is wrong with the child (which means that parents have given me apparently lucid histories of well-defined entities), I have regretted it. (p. 179)

As an example, Carlson described a "7-year-old about to be included in a study of valproate for acute mania" (p. 179), noting it was only the quality of his "aloof" presentation on interview, followed by a day of school observations, that indicated an ASD diagnosis, and not a PBD diagnosis, was correct.

4.8.3.2 **Carlson & Meyer (2006)**

In contrast to diagnoses based on structured clinical interviews as in the COBY study published in the same year (Birhamer & Axelson, 2006), Carlson and Meyer authored a case-study series of PBD-diagnosed children (Carlson & Meyer 2006). By carefully analysing the histories, contextual factors and medication regimes they showed that most of these cases were not bipolar disorder but better described by their comorbid diagnoses in conjunction with affect dysregulation:

> Cross-sectionally, their symptoms of affective dysregulation fit the modified criteria for a manic episode, but from a developmental perspective, it may be more accurate to conceptualize their affective lability as an associated feature of their developmental delays and/or contextual risk factors. (p. 959)

They argued "that bipolar research could benefit from a developmental psychopathology approach." They added: "these children (and adults) need to be better understood, and not simply lumped together because, in the cross section, they all have symptoms of mania." They finished by concluding: "… at the risk of sounding cliché, we quote H. L. Mencken: 'Every complex problem has a solution that is simple, neat and wrong'" (p. 963).

4.8.3.3 **German epidemiological survey investigating CBCL-PBD phenotype**

An epidemiological survey from Germany appeared to accept the PBD hypothesis initially and set out to find cases amongst German children and youth using the same structured clinical interview-based methodology as the MGH-Harvard group. Parents filled out the Child Behaviour Checklist (CBCL) to identify the 'CBCL-PBD phenotype'. The authors commented:

> [T]here is considerable European scepticism about the high prevalence rate of PBD in the USA. Current evidence suggests that PBD is fairly rare outside the USA (Soutullo et al., 2005). In Germany, no epidemiological study has included PBD to date. Despite early descriptions of bipolar children by the German psychiatrist Kraepelin (Kraepelin, 1921), PBD is rarely diagnosed in German clinical samples (Meyer et al., 2004). It seems possible that PBD is not diagnosed as frequently in Europe as in the USA, partly owing to a preference to classify such clinical presentations as severe ADHD, conduct, depressive and personality disorders instead of PBD. (Holtmann et al. 2007, p. 896)

They found a 6-month community prevalence rate of 0.7% in 2,856 German children and adolescents aged 4 – 18-years. The rates varied with age groups: 0.9% in 4 – 7-year-olds; 0.6% in 8 – 11-year-olds; 1.0% in 12 – 15-year-olds; 0.4% in 16 – 18-year-olds. The authors acknowledged it was moot whether this was "real PBD" (p. 899) but advocated recognition on the basis of higher levels of suicidality in the CBCL-PBD cohort.

However, the next year a clinical survey by Holtmann et al. indicated the CBCL-PBD phenotype did not equate with real bipolar disorder (Holtmann et al. 2008). Out of 939 consecutively referred children and adolescents aged 4 – 18-years, only 6.6% (*n* = 62) met criteria for the CBCL-PBD phenotype of whom more than 75% had disruptive behaviour disorders. None of the 62 received a formal diagnosis of bipolar disorder. Two of the 939 patients (0.2%) did receive a diagnosis of bipolar disorder, a 14-year-old girl with a manic episode with psychotic features and 16-year-old girl with Bipolar-II disorder, but neither met the CBCL-PBD criteria. The conclusion: "… the CBCL-PBD phenotype does not correspond with clinical consensus diagnoses of bipolar disorder, but with … severe disruptive behaviour disorders" (160).

4.8.3.4 **Galanter et al. (2012) *JAACAP* critique of structured interviews**

An extensive review of the six structured clinical interviews commonly used "in the application of DSM-IV-TR criteria" for PBD found considerable variability and potential flaws in how the instruments generate PBD diagnoses (Galanter et al. 2012). They attributed the problem partly to ambiguities between the listed diagnostic criteria and explanatory text of DSM-IV-TR, but mostly to the "considerable variation between the diagnostic instruments" (p. 605). The six structured clinical interviews were the KSADS-E (epidemiological version of KSADS); KSADS-PL (present and lifetime version); WASH-U-KSADS; Child and Adolescent

Psychiatric Assessment (CAPA); Diagnostic Interview Schedule for Children, version IV (DISC-IV); and the Missouri Assessment of Genetic Interview for Children (MAGIC).

The CAPA examined past three months, the DSIC-IV past four weeks and lifetime, all the rest cover lifetime. Differences existed in the interviewing of parent and child informants, and in the prompts to lay interviewers in further assessing reported symptoms. Galanter et al. noted significant lack of precision with defining change from usual state with all instruments and with DSM-IV-TR itself. The N = 'no' in table 1 from their article shows the extent of this problem (Figure 4.24). The instruments however were mostly better on linking manic symptoms to co-occurrence with mood episode (Y = 'yes') as in table 3 from Galanter et al. (Figure 4.25).

TABLE 1 *DSM-IV-TR* and Instrument Specifications Regarding Change from Usual State

DSM-IV-TR Criteria for a Manic Episode	Change from Usual State Required													
	DSM-IV-TR		KSADS-E		KSADS-PL		WASH-U KSADS		CAPA		DISC-IV[a]		MAGIC[a]	
	Text[b]	Criteria	Instructions	Questions	Instructions	Questions	Instructions	Questions	Instructions	Questions	Instructions	Questions	Instructions	Questions
A1. Elevated/Expansive Mood	Y	Y	N	N	N	N	N	N	Y	Y	NA	Y	NA	Y
A2. Irritable Mood	Y	Y	N	N	N	N	N	N	Y	Y	NA	Y	NA	Y
B1. Increased Self Esteem[c]	A	A	N	N	N	Y	N[d]	Y	Y	Y	NA	Y	NA	Y
Grandiosity	N	N	N	N	N	Y	N[d]	Y	Y	Y	NA	Y	NA	Y
B2. Decreased Need for Sleep	Y	A	N	Y	Y	Y	Y	Y	Y	Y	NA	Y	NA	Y
B3. More Talkative than Usual[c]	N	Y	N	Y	Y	N	Y	N	Y	Y	NA	Y	NA	Y
Pressure to Keep Talking	N	N	N	Y	Y	N	Y	N	Y	Y	NA	Y	NA	Y
B4. Flight of Ideas[c]	N	N	N	N	Y	N	N	N	N	N	NA	Y	NA	Y
Racing Thoughts	N	N	N	N	Y	N	Y	Y	N	N	NA	Y	NA	Y
B5. Distractibility	Y	N	Y	Y	Y	N	N	N	N	N	NA	Y	NA	Y
B6. Increased Goal Directed Activity[c]	Y	Y	N	Y	Y	Y	N/Y	N/Y	Y	N/Y	NA	Y	NA	Y
Psychomotor Agitation	N	N	Y	Y	Y	Y	N	N	Y	N/Y	NA	Y	NA	Y
B7. Excessive Involvement in Pleasurable Activities, Potential Painful Consequences	Y	N	N	N[e]	N	Y	N	Y	Y	N/Y	NA	Y	NA	Y

Figure 4.24: *DSM-IV-TR* and Instrument Specifications Regarding Change from Usual State (Galanter et al. 2012, p. 609). Reproduced with permission.

TABLE 3 *DSM-IV-TR* B-Criteria Co-Occurrence With Mood Episode

DSM-IV-TR B Criteria for Manic Episode	Co-Occurrence with A-Criterion Required											
	KSADS-E		KSADS-PL		WASH-U KSADS		CAPA		DISC-IV[a]		MAGIC	
	Instructions	Questions	Instructions	Questions	Instructions	Questions	Instructions	Questions	Instructions	Questions	Instructions	Questions
B1. Inflated Self Esteem/ Grandiosity	Y	Y	N	Y	Y	N	Y	Y	NA	Y	Y[c]	Y[d]
B2. Decreased Need for Sleep	Y	Y	N	N	Y	N	Y	Y	NA	Y	Y[c]	N
B3. More Talkative than Usual/ Pressure to Keep Talking	Y	Y	N	Y	Y	Y	Y	N	NA	Y	Y[c]	N
B4. Flight of Ideas or Racing Thoughts	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y[c]	N
B5. Distractibility	Y	Y	Y	Y	Y	N	Y	Y	NA	Y	Y[c]	N
B6. Increase in Goal Directed Activity[b]	Y	Y	Y	N	Y	N	Y	Y	NA	Y	Y[c]	N
Psychomotor Agitation	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y[c]	N
Hypersexuality	Y	Y	Y	N	NA	NA	NA	NA	NA	NA	NA	NA
B7. Excessive Involvement in Pleasurable Activities, Potential Painful Consequences[b]	Y	Y	N	N	Y	Y	Y	Y	NA	Y	Y[c]	N
Hypersexuality	NA	NA	N	N	Y	N	Y	N	NA	Y	Y[c]	N

Figure 4.25: *DSM-IV-TR* B-Criteria Co-Occurrence With Mood Episode (Galanter et al. 2012, p. 614). Reproduced with permission.

The overall message conveyed by Galanter et al.'s thorough critique of the structured clinical interviews is that they are only as good as the experience, intellect and empathic capacity of the interviewers, all of which is complicated by the perspective the interviewer has on the boundaries of bipolar disorder. The authors concluded: "The field of child psychiatry would benefit from more uniform methods of assessing symptoms and determining pediatric BD diagnoses" (p. 605). To this end they made extensive recommendations regarding uniformity of instruments, a high level of training and reliability checking of interviewers, symptoms must be clearly linked to mood episodes that are a marked departure from usual functioning, children must always be interviewed, and "every effort should be made to include information from additional sources about the child's behaviour" particularly from teachers and primary health providers (p. 618).

4.8.3.5 **Playroom based assessment not mentioned in PBD literature**

Galanter's appeal to include information from additional sources still does not include reports from the child in a more naturalistic child friendly setting. While this may be impractical in large scale epidemiological research, it can be vital for accurate diagnosis in individual cases and could be practical for smaller research cohorts.

In reading hundreds of PBD related articles, to the best of my recollection I cannot recall seeing mention of playrooms as a venue and method for child psychiatric assessment, or

therapy for that matter, yet these have been standard practice in child psychiatry. A 'play-therapy room' environment creates a sense of safety and curiosity for children, who can then be more their natural selves. They are more likely to eventually express what truly troubles them, though it may take several sessions of building trust and letting go of defences. Psychiatric symptoms can be more clearly distinguished from what otherwise may be reactive states to strange environments and adult expectations, including structured clinical interview processes.

Accuracy of diagnosis in a 30-minute playroom setting by a child psychiatrist was found to be reasonably robust in an investigation by Sir Michael Rutter (Rutter & Graham 1968). More recently a 2017 textbook, *Psychiatric Interview of Children and Adolescents*, authored by two child psychiatrists from Texas and published by *American Psychiatric Association Publishing* (Cepeda & Gotanco 2017) discusses why the "evaluation of preadolescents" (p. 32) will occur best in a child-friendly environment:

> The child is more likely to feel at ease if the interview is conducted in a specially furnished playroom. The younger the child, the greater the need for nonverbal approaches such as play or the use of nonverbal media (e.g. drawing, puppetry …[etc.]). (p. 34)

This opinion is in concord with traditional perspectives for assessment of children in child psychiatry (Dorfman, 1951).

4.8.4 **Medicating for PBD and concerns over iatrogenic adverse effects**

This section includes a brief synopsis of key articles indicative of how the PBD diagnosis led to increased prescribing particularly of atypical antipsychotics in both the US and Australia, with iatrogenic consequences reported in the literature from both countries.

4.8.4.1 **The medication of very young children spreads**

During the late 1990s and early 2000s, a rapid expansion of the PBD literature occurred, almost entirely supportive of the PBD hypothesis but primarily US based.

Geller and colleagues at WUSL further defined the phenomenology of mania in what they termed a "prepubertal and early adolescent bipolar disorder phenotype (PEA-BP)" (Geller, Zimerman, Williams, DelBello, Bolhofner, et al. 2002). To make this PBD phenotype congruent with "DSM-IV mania" five "cardinal … symptoms (elation, grandiosity, flight of ideas/racing thoughts, decreased need for sleep, and hypersexuality)" were utilised in the WASH-U-K-SADS. This study diagnosed a cohort of 93 78% ultradian cycling 7 – 16-years-old PEA-BP subjects from ADHD subjects, and community control children. This cohort of children and young adolescents would be followed for several years (Chapter 4.8.2.15). In another article from the same year, clearer guidelines for determining manic phenomenology by children were provided, for example:

> Normal children were extremely elated when going to Disneyland, when grandparents were visiting, and on Christmas morning. This mood was appropriate to context, expected by the adults, and non-impairing.
>
> This can be compared to a child who was elated and giggling in the classroom, when others were not, and who got sent to the principal and suspended from school for this behavior. In this example, the elated mood was inappropriate to context and impairing and thus was pathological. (Geller, Zimerman, Williams, DelBello, Frazier, et al. 2002, p. 5)

A growing number of US PBD research centres, including Ohio, Illinois, Texas, California and Utah, published articles on pharmacotherapy trials with PBD cohorts. For example: anticonvulsant mood stabilizers such as topiramate, for 26 subjects of mean-age 14-years (DelBello, Kowatch, et al. 2002) and "topiramate plus risperidone for controlling weight gain and symptoms in preschool mania" (Pavuluri, Janicak & Carbray 2002); divalproex sodium for forty 7 – 19-year-olds (Wagner et al. 2002); divalproex sodium and lithium combination for 90 subjects mean-age 10 (Findling et al. 2003), and a similar combination study for 35 subjects mean-age 11 (Kowatch et al. 2003). Further studies examined atypical antipsychotics such as quetiapine for 30 manic adolescents (DelBello, Schwiers, et al. 2002a); quetiapine for 32 subjects of mean-age 10 (Marchand, Wirth & Simon 2004); risperidone in combination with lithium or divalproex sodium for 37 subjects of mean-age 12 (Pavuluri, Henry et al. 2004); and ziprasidone for four patients aged 7 – 16-years in private practice (Barnett 2004). In short, by

the early 2000s, cohorts of pre-pubertal children were being gathered across the US for pharmacotherapy studies of the PBD hypothesis.

Invariably these trials found the atypical antipsychotics and anticonvulsant medications to be 'effective' and 'well tolerated' for symptoms of 'paediatric mania'. A typical conclusion paragraph from an article's abstract read:

> The findings of this study indicate that quetiapine in combination with DVP [divalproex] is more effective for the treatment of adolescent bipolar mania than DVP alone. In addition, the results suggest that quetiapine is well tolerated when used in combination with DVP for the treatment of mania. (DelBello, Schweirs, et al. 2002, p. 1216)

Articles describing preschool PBD cohorts also began to be published from several US states. The MGH-Harvard group as mentioned above studied 44 pre-schoolers who reportedly had onset of symptoms at a mean age of 2.5-years-old (Wilens et al. 2002). Fristad and colleagues (Ohio State University) reported six cases out of 36 consecutive child psychiatric admissions between ages 3 – 5 had PBD, of which "five received lithium and … improved", concluding that "preschool mania exists as an identifiable entity" (Tumuluru et al. 2003). A PBD clinic in Wisconsin reported treating 31 patients aged 2 – 5-years-old, primarily with valproic acid and that "treatment with mood stabilizers was clinically effective, with corresponding significant developmental benefits" (Scheffer & Apps 2004). The authors' conclusions served to reflect that this was now apparently an era of psychotropic medicating of toddlers and pre-schoolers in the US:

> Twenty-one of the 31 patients reported prior treatment attempts with either a stimulant or antidepressant without the protective benefit of a mood stabilizer, and of these, 13 (62%) reported a worsening of mood symptoms during that treatment period. (p. 489)

An article in the *Journal of Affective Disorders* co-authored by the chief-editor, Akiskal, was a case series of "11 of 40 (27.5%) presenting children below the age of 5 years who met the criteria for mania" from a Texas child mental health clinic (Dilsaver & Akiskal 2004). Severe emotional and behaviour dysregulation were described in the vignettes and familial history of mood disorder diagnoses was common. The authors describe using valproate for two 3-year-olds and one 4-year-old to achieve "complete and full responses" (p. S41), as well as

other medications. Two cases relapsed after valproate was ceased following abnormal liver function tests, and on recommencement in one boy, valproate failed to achieve the prior beneficial response.

It is clear from this sample of publications that the concept of bipolar disorder commonly first presenting in preschool children, necessitating pharmacotherapy, was infiltrating mainstream practice in US child psychiatry.

4.8.4.2 **Data published of paediatric atypical antipsychotic prescribing**

4.8.4.2.1 **Olfson et al. (2015) atypical antipsychotic paediatric prescription data**

Atypical antipsychotic prescribing in the paediatric age range in the US was quantified by Olfson et al. (2015). According to IMS Health data atypical antipsychotics were prescribed to forty-two thousand four hundred fifty-nine 1 – 6-year-olds; two hundred twenty thousand three hundred five 7 – 12-year-olds; and three hundred five thousand one hundred sixty-five 13 – 18-year-old US children and teens in 2006 (p. 869). Rates for the youngest cohort were roughly 15% higher in 2008 before falling to roughly 25% lower than the 2006 rate by 2010 following new pre-authority prescribing laws, though adolescent rates continued to climb.

The majority of scripts were for boys with ASD or disruptive behaviour disorders including ADHD. Eight percent of scripts for 1 – 6-year-olds were for bipolar disorder, as were 13% of scripts for age 7-12 and 20% of scripts for ages 13-18. The PBD era, coinciding with the atypical anitpsychotic era of the last two decades, has been associated with perhaps two million or more children and adolescents receiving atypical antipsychotics during their development, although many did not receive a formal bipolar diagnosis.

4.8.4.2.2 **Lohr et al. (2015) antipsychotic prescribing to under-7s in Kentucky**

A study of Medicaid data for prescriptions of atypical antipsychotics to children aged 6-years and under, for the decade from 2001 to 2010 revealed high rates (Lohr et al. 2015). A total of 6,915 children received a prescription for an atypical antipsychotic during this time. Children received an average of 10 scripts each, with an average 0.75% of all under-7-years-old children being treated, with a peak of 1% in 2004 and 2.4% of 6-year-old children receiving an atypical antipsychotic. Boys received 73% of the atypical antipsychotics. Lohr et al. found

that after Medicaid stipulated prior authorisation based on diagnosis in 2006, that: “Mood disorders (predominantly bipolar disorder) accounted for almost 75%” (p. 441).

Prescribing rates by every county across the state of Kentucky (Lohr et al. 2015, online supplementary figure 3) were also provided. These showed marked variation in the percentage of Medicaid infants, toddlers and children to the age of 6-years-old taking atypical antipsychotics – from as low as 0.24% to as high as 2.43%. Such variation is a hard data indication of the anecdotal reports that many US clinicians were sceptical of diagnosing pathology such as PBD in young children.

4.8.4.3 Iatrogenic significance of antipsychotic prescribing: cardiac arrests, cerebral atrophy, metabolic adverse effects

It is worth mentioning that these atypical antipsychotic prescription figures are concerning in the light of: well-known rapid weight gain and metabolic changes including hyperprolactinaemia (Biederman, Mick, Hammerness, et al. 2005; Chapter 3.3.1), sensitivity of young children to EPSE (Wonodi et al. 2007; Zito et al. 2008; Strayhorn 2006; Chapter 4.6.4), haematological and hepatic adverse events, cardiac arrest due to prolongation of the QTc cardiac electrical conduction interval (Ray et al. 2019), and adult human and juvenile animal studies showing possible cerebral atrophy (Bastiampillai, Parry & Allison 2019; Appendix A32). The concerning numbers of paediatric mortality cases where an atypical antipsychotic is listed as ‘primary suspect’ in the FAERS reporting data (Elias, 2006; Harris, J 2008; Chapter 4.6.4) receives more credence from these figures of widespread use in very young children.

4.8.4.3.1 Ray et al. (2019 – published online 2018) *JAMA Psychiatry*

A large and methodologically detailed study of new users of psychotropic medications found an increased odds ratio of 3.5 for all causes of unexpected non-overdose deaths and 4.29 for death from cardiac or metabolic cause while on antipsychotic medication compared to a control group on other psychotropic medications (Ray et al. 2019). The study cohort were children and youth aged 5 to 24 years, who were enrolled in Medicaid in the state of Tennessee during the period 1999 through 2014. The study “excluded patients with life-threatening somatic illnesses” to not obscure causes of mortality (p. E2).

The study looked at new users of psychotropic medication. The control group of 189,361 children and youth were on non-antipsychotic psychotropics such as stimulants, antidepressants or anticonvulsants. The increased mortality from cardiac arrests was hypothesised as mostly due to arrhythmia related deaths from QTc prolongation in cardiac conductivity, and evident in the group of 30,120 new users of antipsychotics above a 50 mg chlorpromazine dose equivalent. This dose is equivalent to 1mg risperidone, 2.5mg olanzapine, 3.75mg aripiprazole, 37.5mg quetiapine. These are common doses in behavioural paediatrics. Ray et al. cite Olfson et al. (2015) and Correll and Blader (2015) for a figure of 1.3 million individuals aged 24 or younger on antipsychotic medication in 2010 in the US. Therefore, these iatrogenic mortality figures pose a public health hazard.

4.8.4.3.2 Increasing use of atypical antipsychotics in paediatrics in Australia

Prescribing of antipsychotics for off-label sedation of disruptive behaviour is a growing world-wide problem. Recent data from Australia indicated a 24% and accelerating increase in children and adolescents under age 17 prescribed antipsychotics from 2013-14 to 2017-18 to a total of 24,700 (Magery 2018). In 2016, 1,300 were aged 2 – 6-years-old and 6,000 aged 7 – 11-years-old. In Australia these prescriptions are mostly given for disruptive behaviour associated with ASD or ADHD, or what might be termed DMDD in DSM-5 parlance.

4.8.4.3.3 Bastiampillai et al. (2019) *ANZJP*

A further concerning problem with widespread use of atypical antipsychotics, and sometimes older 'first-generation antipsychotics', in the paediatric age range, is the possibility of causing cerebral atrophy and retarding natural brain growth. We authored a review of animal studies and adult psychiatric literature suggesting this to be the case in the *ANZJP* (Bastiampillai, Parry & Allison 2019; Appendix A32).

Macaque monkeys administered haloperidol or olanzapine demonstrated significant total brain volume loss of approximately 8-11% after 17-27 months of exposure to haloperidol or olanzapine, compared with sham medication controls (Dorph-Petersen et al. 2005). These findings were replicated in a study of adolescent rats (9 weeks old) with a 6-8% volume loss after 8 weeks of haloperidol or olanzapine, compared to sham medication controls (Vernon

et al. 2011). Most brain volume loss was in the frontal and parietal lobes in these animal studies.

Importantly, the findings were replicated in a large human cohort study of 211 patients with first episode schizophrenia. Ho et al. (2011) found that greater intensity (higher dose and longer duration) of antipsychotic treatment was associated with statistically significant brain volume loss, even after controlling for illness duration, illness severity and substance abuse. The authors specifically warned clinicians about the potential for brain volume changes when prescribing atypical antipsychotics for non-schizophrenic disorders. There are no studies of the long-term effects of antipsychotics on brain volumes among patients without schizophrenia, but Ho et al. concluded "our results suggest that antipsychotics should still be used with caution in these patient groups after careful risk-benefit assessment" (page 135).

4.8.5 **The evolution of a new DSM-5 diagnosis: DMDD**

4.8.5.1 **Emergence of the SMD concept**

As indicated by the first two '10-year reviews' on PBD in *JAACAP*, there were growing expectations that the PBD hypothesis would be more formally reified into a diagnostic entity in DSM-5. However, the growing controversy in the media and the academic literature as to the iatrogenic consequences of an overdiagnosis epidemic of childhood bipolar disorder, following the death of Rebecca Riley, saw the emergence of a new descriptive label for severe childhood emotional and behavioural dysregulation. Initially, this was coined as 'Severe Mood Dysregulation' (SMD) disorder, then 'Temper Dysregulation with Dysphoria' (TDD), and finally inaugurated as 'Disruptive Mood Dysregulation Disorder' (DMDD) into the DSM-5 by time of the APA's 166th meeting in May, 2013.

The inclusion of DMDD was specifically designed to subsume 'broad phenotype' PBD. It had been a deliberate and rapid program to create the new diagnostic category, led by a single group of researchers collaborating with Professor Ellen Leibenluft, chair of the DSM-5 paediatric mood disorders committee and based at the NIMH. In 2010, at the Hastings Center, Leibenluft noted that DSM-5 would likely be accepting SMD as TDD (Parens & Johnston 2010). By 2011, even *Medscape*, a traditionally pro-PBD continuing medical education platform, had

acknowledged that SMD should replace 'broad' phenotype PBD. This section covers a range of years, summarising the history of the new disorder but concludes with how 'broad' phenotype PBD is proving resistant to being renamed.

4.8.5.2 **Teasing out SMD from 'narrow' phenotype PBD**

As described in Chapter 4.5.1 above, Leibenluft, and her colleagues at the NIMH had published research defining a cohort of 'SMD' children and youth (Brotman et al. 2006). The key finding was as these children and adolescents entered adulthood, they had elevated rates of depression and personality disorders, but not of mania. This was confirmed in a 20-year community prospective longitudinal study (Stringaris et al. 2009) and in a specific sample of 84 SMD youth versus 93 youth with "DSM-IV bipolar disorder" followed over a median 28.4 months. In the latter study only one patient with SMD (1.2%) exhibited a new manic/hypomanic/mixed episode, whereas 58 (62.4%) of the bipolar disorder group did. The mean age at baseline was 11.6 (SD 2.3-years) for SMD group and 12.9 (SD 2.8-years) for the bipolar disorder group (Stringaris, Baroni et al., 2010).

The researchers said they had defined the bipolar disorder group narrowly, in line with DSM-IV Bipolar-I and Bipolar-II criteria including duration criteria. However, in similar research style to the WUSL group, Leibenluft, Stringaris and colleagues had based diagnoses on K-SADS interviews, that have been critiqued for vagueness at defining episodes and double counting symptoms to different disorders (Carlson 1998; Carlson & Klein, 2014; Carlson 2018; Galanter et al. 2012). The findings may explain why Leibenluft had written the supportive *Archives of General Psychiatry* editorial (Leibenluft 2008) for Geller et al. (2008)'s ultradian cycling "Bipolar I disorder" cohort. Rates of comorbidity were high: The bipolar disorder group had comorbidities of ADHD 45.2%, ODD 25.8%, CD 2.2%, Generalized Anxiety Disorder (GAD) 32.3%; and not recorded for MDD; the SMD group's comorbidities were ADHD 82.1%, ODD 78.6%, CD 4.8%, GAD 29.8%, MDD 22.6% (Stringaris, Baroni et al. 2010).

Therefore, while showing that broad phenotype PBD, i.e. SMD, does not progress to bipolar disorder, Stringaris, Baroni et al. (2010) does seem to find a group of 93 peripubertal/early adolescent children with Bipolar-I or Bipolar-II disorder. This may reflect the extensive resources of the NIMH to recruit research cohorts. Alternatively, the methodology, much the same as widely used in PBD research, is dissimilar to the way diagnoses of hypomania/mania

and bipolar disorder are customarily made in clinical practice by psychiatrists both within and outside the US. That is, getting to know the child or young adolescent in their psychosocial context, observing mental state changes over several clinical interviews, and using 'pattern recognition' clinical skills rather a solely checking criteria approach (Dubicka et al. 2008).

Further, basing all the follow-up interviews on parent report alone (by telephone) does create the possibility of false positive bias towards bipolar diagnoses by parents given belief in widespread bipolar within the US. This belief is sustained by DTCA about bipolar disorder, and the general high diagnosing levels by clinicians.

Ongoing debates over 'narrow phenotype' bipolar disorder aside, Leibenluft and colleagues seem to have successfully debunked 'broad phenotype PBD'. This point was emphasised in a major "Practitioner review: the assessment of bipolar disorder in children and adolescents" (Baroni et al. 2009):

> The nosological status of youth with non-episodic, impairing irritability is unclear. However, the currently available genetic, physiological, and natural history data do not support assigning them a diagnosis of BD. (pp. 212-213)

Leibenluft and colleagues were keen to set this in stone and being positioned at the NIMH with direct oversight of the committee for mood disorders assisted the incorporation of SMD into DSM-5.

4.8.5.3 **SMD to become Temper Dysregulation with Dysphoria (TDD)**

The initial proposed name for the soon to be canonised DSM-5 disorder was Temper Dysregulation with Dysphoria Disorder (TDD). The APA produced a draft document on the rationale for TDD that was accessed in March 2013 at http://www.dsm5.org/Proposed%20Revision%20Attachments/Justification%20for%20Temper%20Dysregulation%20Disorder%20with%20Dysphoria.pdf, although no longer on the DSM-5 website by 29 August 2013. The draft had confirmed the primary 'justification' for the new disorder was the over-diagnosis of PBD in the US:

> **I. Explication of the reason for a proposed change**
>
> *A. Background:*

> One of the most dramatic developments in child psychiatry in the past decade has been a marked upsurge in the rate at which children are being assigned the diagnosis of bipolar disorder (BD) (Moreno et al., 2007; Blader and Carlson, 2007). …
>
> *B. Rationale for introducing a diagnostic category for temper dysregulation with dysphoria (TDD) within the mood disorders section of DSM-V:*
>
> As noted above, within the last decade a school of thought has developed amongst some researchers and clinicians that severe, non-episodic irritability is characteristic of pediatric BD. That is, the contention has been that mania manifests in youth, not episodically as in DSM-IV, but instead as severe, non-episodic irritability (Biederman et al., 2004; Mick et al., 2005). Given the upsurge in the rate of the diagnosis of pediatric BD, and the question as to whether severe, nonepisodic irritability should be viewed as a developmental phenotype of pediatric BD, research over the past 8 years has compared youth with such irritability to those with episodic DSM-IV BD. To facilitate this research, a syndrome called severe mood dysregulation (SMD) was defined …

It is worth noting here that PBD was never a significant problem outside the US, but the new diagnosis was needed to counter the US PBD epidemic. As the DSM is the publication of the American Psychiatric Association such a change can be justified. However, the necessity of such a diagnostic category for usage outside the US remains questionable.

TDD created quite a deal of controversy: PBD researchers felt it would detract from PBD research and clinical practice (Axelson 2010); critics felt it further over-medicalised childhood (Frances 2010a). Both published critical articles in *Psychiatric Times*. Axelson's was titled "Adding the diagnosis of Temper Dysregulation Disorder to DSM-5: Do we really need it?", while Frances' was named: "DSM-5 Temper Dysregulation: Good intentions, bad solution". Axelson and Frances agreed on several points: that irritability is by far too common a symptom across a vast number of DSM disorders of childhood and adolescence so creating a new disorder based on a single symptom risked even more diagnostic confusion; secondly that the research base for TDD was small and un-replicated.

Axelson and colleagues outlined the heterogeneity of irritability:

> [T]he symptom of irritability is a DSM-IV diagnostic criterion for a range of psychiatric disorder categories: bipolar disorder, major depressive disorder, dysthymic disorder, cyclothymic disorder, generalized anxiety disorder, posttraumatic stress disorder, acute stress disorder, and oppositional defiant disorder (ODD). In addition, irritability (with temper outbursts) is commonly present in other disorders such as attention-deficit/hyperactivity disorder (ADHD), conduct disorder, separation anxiety disorder, autism spectrum disorders, reactive attachment disorder, psychotic disorders, and substance use disorders and in children who have been maltreated or abused or those who have suffered brain injury from trauma, developmental insults, or in-utero exposure to drugs or alcohol. … Temper dysregulation with dysphoria does not have other symptoms or criteria that are unique to the TDD diagnosis. (Axelson, Birmaher, Findling, et al. 2011, p. 2)

The authors acknowledged "the overarching reason for the creation of" TDD was "the perceived marked over-diagnosis of bipolar disorder in youth" (p. 5). However, they felt the over-diagnosis problem was over-stated. They recommended a subcategory of ODD with extreme irritability. They further stated:

> In addition, including the TDD diagnosis in the DSM-5 would likely spur the pharmaceutical industry to seek FDA approval for TDD as an indication, resulting in the substantial expansion of use of medications for youths with irritability. (p. 8)

Elsewhere, the director of CABF/Balanced Mind Foundation, Susan Resko, expressed concerns that TDD would overshadow PBD and lead to parents being blamed for being unable to "control their bratty kids" (Miller 2010).

Frances agreed with Axelson et al. that irritability is "a single symptom, not a complete syndrome". He advocated a similar solution: creating a specifier of explosive outbursts that could be added to other disorders, in particular ODD. He acknowledged the good intentions that "something clearly needed to be done" to correct the "wild over-diagnosis of childhood bipolar disorder" (Frances 2010a; para. 1) but was concerned at the much greater problem of pathologizing childhood:

> [T]here is enormous variability in what are considered appropriate expressions of temper across kids, across developmental periods, across families, and across subcultures. The definition of "severe" will likely vary greatly depending on the tolerance of the clinician, family, school, and peer group. … Family fights that are based in interpersonal problems will be translated into individual psychopathology. Finally, in the heat of battle, it will be forgotten that kids often do outgrow a developmentally or situationally triggered temperamental period in their lives. (para. 8)

Instead of the APA adding TDD to the DSM, Frances advocated for an education campaign towards psychiatrists, physicians and the general public:

> [T]o highlight the risks of overuse of atypical antipsychotics and to recommend caution in diagnosis and treatment of kids with temper outbursts (Frances 2010a).

4.8.5.4 **DSM-5 settles on TDD but renames it DMDD**

Despite the opposition to TDD, the construct was accepted into DSM-5, albeit with a name change – given the criticism that tantrums were being labelled as a psychiatric disorder the word 'temper' was removed. Thus, Disruptive Mood Dysregulation Disorder, with the customary acronym being DMDD, entered the APA's diagnostic manual. The criteria were perhaps most succinctly summarised by The Balanced Mind Foundation in a blogpost alerting parents of PBD children to the new diagnosis and acknowledging their confusion and possible distress, since presumably for many parents the PBD label had become a source of certainty amongst their worries with their children. The criteria for DMDD were listed (Resko 2012):

> A. Severe recurrent temper outbursts that are grossly out of proportion in intensity or duration to the situation.
>
> B. The temper outbursts are manifest in the form of verbal rages or physical aggression towards people or property.
>
> C. The temper outbursts are inconsistent with developmental level.
>
> D. The temper outbursts occur, on average, three or more times per week.
>
> E. Nearly every day, most of the day, the mood between temper outbursts is persistently irritable or angry.

F. The irritable or angry mood is observable by others (e.g., parents, teachers, peers).

G. The diagnosis should not be made for the first time before age 6 or after age 18.

H. The onset of these symptoms is before age 10 years.

I. There has never been a distinct period lasting more than one day during which abnormally elevated or expansive mood was present most of the day, and the abnormally elevated or expansive mood was accompanied by the onset or worsening, of three of the criteria of mania (such as grandiosity or inflated self-esteem, decreased need for sleep, pressured speech, flight of idea, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences).

J. The behaviors do not occur exclusively during an episode of Major Depressive Disorder and are not better accounted for by another mental disorder. The symptoms are not due to the effects of a drug or to a general medical or neurological condition.

The new DSM-5, launched at the APA San Francisco conference in May 2013, listed the same criteria for DMDD almost word for word. A 'K' criteria was added that DMDD symptoms be "not attributable to the physiological effects of a substance or to another medical or neurological condition" and exclusion criteria were that DMDD cannot coexist with ODD, intermittent explosive disorder, or bipolar disorder, though it can coexist with other disorders, including MDD, ADHD, CD and substance use disorders (APA 2013a).

4.8.5.5 **TDD/DMDD in research 2012-13**

The DMDD diagnosis met with resistance from many PBD researchers. Biederman et al. had implicitly criticised its penultimate iteration as TDD in their *NEJM* letter (Biederman, Wozniak & Faraone 2010) responding to Parens, Johnston and Carlson's lukewarm approval of TDD (Parens, Johnston & Carlson 2010). Research groups adherent to a more 'narrow' phenotype PBD hypothesis, especially in Pittsburgh, Ohio, University of North Carolina and Stanford University, evaluated the DMDD criteria within their multi-centre Longitudinal Assessment of Manic Symptoms (LAMS) study. Their analysis led them to conclude:

> DMDD could not be delimited from oppositional defiant disorder and conduct disorder, had limited diagnostic stability, and was not associated with current, future-onset, or parental history of mood or anxiety disorders. These findings raise concerns about the diagnostic utility of DMDD. (Axelson et al. 2012, p. 2)

Also in 2012, Carlson and colleagues assessed the DMDD criteria for 82 consecutive admissions to a pre-teens' psychiatric inpatient unit. They found parent structured clinical interview report doubled the clinician's diagnostic rate, while still keeping half the PBD diagnoses. Yet only two of the 82 children (ages 11 and 12) had confirmed bipolar disorder by discharge (Margulies et al. 2012). The opposition by many PBD researchers, and this finding by Carlson's group did not suggest an optimistic future for DMDD.

Despite being yet another reified set of behaviours, DMDD seems to be entering the US public consciousness. As such it conveys awareness of an over-diagnosis problem with PBD, and that individual and family therapy approaches may have more impact than medication, at least judging by an article at *Healthline.com* (Browne & Legg 2017):

> Helping children with DMDD may involve psychotherapy or behavioral interventions, medication, or a combination of both. Non-medication treatments should be explored first … During psychotherapy, parents and children meet with a therapist every week to work on developing better ways of relating to one another. (para. 29-30)

On the other hand, in the six years since its launch, the DMDD diagnosis has hardly been used here in Queensland, Australia. For example, a question to the email list of Queensland child psychiatry colleagues in July 2019 revealed just one DMDD diagnosis in a recent immigrant family from the US, and one other diagnosis made by a local child psychiatrist.

4.8.5.6 **'Broad' phenotype PBD still being published**

Four years after the DSM-5 launched DMDD, the MGH-Harvard reported on familial characteristics of children and adolescents with "full and subsyndromal pediatric bipolar disorder" in *Bipolar Disorders* (Wozniak et al., 2017, p. 168). This long-running study compared first degree relatives of those with "subthreshold pediatric bipolar I disorder" and "full" "pediatric bipolar-I disorder" with relatives of patients with ADHD and normal control children and youth (p. 168).

In contrast to the high-risk offspring studies, Wozniak and colleagues were reporting on a much younger age group with high ADHD comorbidity, in a large cohort ('Full BP-I' 239; 'Subthreshold BP-I' 43; 'ADHD' 162; 'Controls' 136), and their mean age (10½-years, with SD > 3 years) meant at least half were pre-pubertal. The number of first-degree relatives totalled over 1,700 (p. 168).

Consistent with previous MGH-Harvard group studies, diagnoses had been made by "trained and supervised psychometricians" (p. 170) using the K-SADS-E, "with clinical assessment by an expert child and adolescent psychiatrist" (p. 174) with a "97% agreement" (p. 170) identified as the lead author in an earlier report (Wozniak et al., 2003).

In contrast to the MGH-Harvard group's earlier work, the 'broad' chronically irritable PBD phenotype was not described in such terms. This cohort of "full" 'Bipolar-I disorder' cases was defined on the basis of strict DSM-IV criteria:

> For BP-I, the DSM-IV required subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive, or irritable mood lasting at least 1 week, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance. (p. 171)

Therefore, many readers would presume this was a cohort of children and teens with classical manic episodes. As indicated in Figure 4.26, which was Table 2 from Wozniak et al. (2017) the 'BP-I' cohort were emotionally and behaviourally dysregulated, meeting on average criteria for eight DSM-IV diagnoses.

	BP-I ($n=157$) n (%)	ADHD ($n=162$) n (%)	Control ($n=136$) n (%)	Statistic
Psychosis	51 (33)	–[c]	–[c]	
Major depression	131 (83)[a,b]	61 (37)[a]	10 (7)	$\chi^2(2)=175.5$, $p<0.001$
Multiple (2) anxiety disorders	100 (64)[a,b]	43 (27)[a]	6 (4)	$\chi^2(2)=120.7$, $p<0.001$
ADHD	133 (85)	–[c]	–[c]	
Oppositional defiant disorder	141 (90)[a,b]	87 (54)[a]	8 (6)	$\chi^2(2)=205.9$, $p<0.001$
Conduct disorder	80 (51)[a,b]	24 (15)[a]	2 (2)	$\chi^2(2)=109.9$, $p<0.001$
Substance (alcohol or drug) use disorder (abuse or dependence)	18 (12)[a,b]	5 (3)	1 (1)	$\chi^2(2)=19.2$, $p<0.001$

Figure 4.26: Psychiatric co-morbidity in children (Wozniak et al., 2010, p. 1083). Reproduced with permission.

Seven years earlier this PBD cohort was described in more familiar detail (Wozniak et al., 2010). The children had a mean age of bipolar onset as first graders with a standard deviation extending down to 2½-year-olds, and presented with the chronic rapidly cycling picture:

> The clinical presentation of BP-I disorder in probands was characterized by early onset (5.8 ±3.4 years), rapid cycling (22.4 ±61.6 episodes) and a chronic course (3.6 ±3.3 years in duration). (Wozniak et al. 2010, p. 1083)

Wozniak and colleagues (2017) extensively quote from the Pittsburgh group's longitudinal COBY and BIOS offspring studies, citing nine references in total, but there was no reference at all to the Canadian, Dutch, Swiss, Amish or Indiana University offspring studies.

They claimed a "commonly seen" rate of subthreshold PBD equated with Lewinsohn et al.'s (1995) upper figure of 6%, and stated:

> Affected children with such pre-syndromatic states are commonly seen in the clinic (Safer et al., 2015, Correll et al., 2014). (p. 169).

However, one of the references cited, Safer et al. (2015), concluded the increase in subsyndromal NOS diagnoses in US clinical practice was an over-diagnosis problem with iatrogenic consequences, quite contrary to Wozniak et al.'s claim.

Quoting an enormous statistical increase in Bipolar-NOS diagnoses in US clinical practice during the first decade of the 21st century, Safer et al. (2015) had written:

> Among visits for bipolar disorder, NOS visits increased more than 18-fold, from 3.6% in the 1999-2002 period to 72.6% in the 2007-2010 period ($P < .001$). In addition, anxiety disorder NOS increased from 44.6% in the 1999-2002 period to 58.1% in the 2007-2010 period.

Safer et al. made it very clear that this extreme increase in DSM-IV-NOS visits, particularly for bipolar, was not a desirable outcome:

> **Conclusions and Relevance:** … Unspecified diagnoses lack research reliability and potentially increase the likelihood of off-label prescribing of psychotropic medication.

With regard to the "6%" rate, Wozniak et al. (2017) cited an epidemiological study from 1988 (Lewinsohn et al., 1995). Lewinsohn et al. had followed that adolescent cohort into young adulthood (Lewinsohn et al., 2000a, Lewinsohn et al., 2002, Lewinsohn et al., 2003). Wozniak et al. failed to report that the 5.7% of subsyndromal Bipolar-NOS cases did *not* continue as bipolar cases in the follow-up studies (Parry, Allison & Bastiampillai 2018a; Appendix A31; Chapter 6.5.2.2)

Thus, the findings of Lewinsohn et al. reflect the classical perspective. The vast majority of subsyndromal affect lability is not bipolar disorder. The reporting of this research by Wozniak et al. (2017) would lead readers to an erroneous conclusion.

It is surprising that this article, in the flagship journal of the ISBD, was allowed to use the term 'Bipolar-I disorder' for their PBD cohort. It was published four years to the month after DSM-5 and the new diagnosis of DMDD which seems a more accurate description of the MGH-Harvard PBD cohort. It can be argued, as implied by Post et al. (2017), that research to examine family dynamic, parent-child attachment, maltreatment, and trauma variables is needed to help elucidate the origin and perpetuating factors for such symptomatology. MGH-Harvard have a very large cohort and are well resourced; such research could well be very valuable.

4.8.6 **International perspectives on bipolar disorder in children and youth**

As indicated in the Prologue, and to be explored in a systematic literature review in Chapter 7, the PBD hypothesis mostly failed to gain momentum outside the US. As the following selected literature review shows, there were early expectations of international spread but opinion surveys of child psychiatrists in Germany, the UK, Australia and New Zealand, as well as data on international diagnostic rates, show that the classical, conservative view of bipolar disorder generally held sway in non-US jurisdictions.

4.8.6.1 **PBD spreads beyond the United States**

During the early 2000s, non-US articles started to appear. In particular, Akiskal co-authored with Masi and colleagues from the University of Pisa, Italy (Masi et al. 2001, Masi et al. 2004),

and DelBello and colleagues with Soutullo from the University of Navarre, Spain (DelBello et al. 2001, Soutullo et al. 2002). These Italian and Spanish researchers fully adopted the pro-PBD hypothesis and methodologies of the US PBD researchers.

As a sign of the growing enthusiasm for PBD in the academic literature, in November 2003 Biederman was guest editorialist in a special PBD-themed issue of *Biological Psychiatry*. Biederman stated that pre-pubertal mania is atypical, common, under-diagnosed, and diagnosable by "trained psychometricians" with 97% agreement with clinicians. Referring to the articles within the special issue, Biederman asserted that modification of the Child Behaviour Checklist (CBCL) can detect cases such as 7% of a clinical sample of pre-pubertal Brazilian children. He described offspring studies identifying "prodromal signs" in children and "temperamental antecedents" of CD symptoms in toddlerhood; that familial studies suggest a genetic linkage of bipolar disorder and ADHD; postulated neuropathological correlates in "cortico-limbic-striatal circuits"; pharmacotherapy for PBD modelled on adult bipolar disorder protocols; and psychoeducation modules for families. Biederman concluded:

> [I]t is hoped that such explosive developments in neurosciences, neurobiology, genetics, neuroimaging, and therapeutics will help advance the understanding and treatment of this complex and crippling disorder. (Biederman 2003, p. 933)

One of the articles in this special issue, "Pediatric bipolar disorder: The parent advocacy perspective", was

Articles sceptical of PBD perspectives were still lacking in the child psychiatric literature during this time. However, a 2003 article in *JAACAP,* by McClellan and co-author Werry from NZ, although not focussing explicitly on PBD, briefly mentioned there was a controversial rise in youth bipolar diagnoses. They cautioned that child and adolescent psychiatry was an inexact science and prone to fad diagnoses:

> [W]e still suffer faddish waves of unsupportable treatments and idiosyncratic practices; caution and humility are indicated when assessing our standards of care. (McClellan & Werry 2003)

This scepticism was also illustrated in an editorial titled "Bipolar-spectrum disorders: An epidemic unseen, invisible or unreal?" in the British based *Advances in Psychiatric Treatment*

(Bhagwagar & Goodwin 2004). The authors, from Oxford University, UK, referred to the PBD 'epidemic' in an overview of increased bipolar disorder diagnoses in both adult and paediatric populations. While sympathetic to the view that milder cases of hypomania were being missed in adults, the authors cautioned that "diluting the concept (with a widened bipolar spectrum) will lead to a trivialisation of the disorder" (p. 2). As for PBD being a US phenomenon, they were less circumspect:

> Its existence has been questioned with a British epidemiological study finding no case of mania among pre-adolescent children (Meltzer et al, 2003). The contrast with North American enthusiasm for bipolar diagnoses in children is striking (p. 2).

They raised another controversy that does require further research, namely:

> [T]he treatment of ADHD with stimulants may have the potential to induce elated states in children. Is it possible that the widespread use of stimulants to treat difficult behaviour in children accounts for the apparent epidemic of paediatric bipolar disorder in North America? (p. 2)

Scepticism was also noticeable in Germany. A survey of child psychiatrists in outpatient practice (Meyer, TD, Kossmann-Bohm & Schlottke 2004) found adherence to the classical perspective. Of 251 child and adolescent psychiatrists (a 61% response rate), only 7.8% had ever diagnosed a child under age 12 with bipolar spectrum disorder (ICD-10 diagnoses of manic episode, bipolar disorder and cyclothymia), while 63% had diagnosed adolescents aged 12 – 16-years-old. German child psychiatrists were more likely to diagnose bipolar spectrum disorder if they were younger and described their practice as mainly 'pharmacological' and non-psychodynamic. In a sign that the PBD hypothesis' prominence in the literature was having a global effect, the authors cited US PBD research to suggest that German clinicians were underdiagnosing bipolar disorder.

4.8.6.2 **The British NICE guidelines**

In the UK, clinicians were aware of the differing criteria being used in the US to make the PBD diagnosis and were concerned about trans-Atlantic spread. The British National Institute for Health and Clinical Excellence (NICE) is the preeminent body within the UK for setting clinical guidelines, and in 2006, NICE commissioned the Royal College of Psychiatrists Research and

Training Unit to produce guidelines covering the diagnosis and management of bipolar disorder (NICE 2006).

The document stated that pre-pubertal bipolar disorder is "very rare" and adolescent bipolar disorder is "rare". They advocated for strict use of Bipolar-I disorder criteria as per DSM-IV and ICD-10 and stated that Bipolar-II disorder diagnosis should not be made except perhaps in developmentally mature adolescents. Irritability as a core criterion was specifically excluded. The guidelines discuss use of Bipolar-II and Bipolar-NOS as appropriate in research settings but "were not convinced that evidence currently exists to support the everyday clinical use of (these) diagnoses" which increase the "risk that medicines may be used inappropriately to treat a bipolar diathesis that does not exist." (p. 526). Lack of symptom specificity during development was the issue and other diagnoses and environmental factors including abuse should be considered first. They cautioned against use of rating instruments such as the WASH-U-K-SADS and advised British clinicians to make a thorough clinical assessment before diagnosing the rare case of a pre-pubertal child with mania, and to consider "sexual, emotional and physical abuse if they show disinhibition, hypervigilance or hypersexuality" (p. 40). It is possible that such advice, if followed, may well have been life-saving later that year across the Atlantic in Boston.

4.8.6.3 **Editorials convey debate over PBD validity**

During 2007, three major national psychiatric journals, the *American Journal of Psychiatry*, *The Canadian Journal of Psychiatry*, and the *Australian and New Zealand Journal of Psychiatry (ANZJP)*, all covered the PBD phenomenon. The editorials either acknowledged or precipitated debate.

4.8.6.3.1 **Editorial in the *American J Psychiatry***

The controversial nature of PBD featured in an editorial in the *American Journal of Psychiatry*:

> Paediatric bipolar disorder is notoriously controversial, with the epicentre of the debate being whether the condition can be diagnosed in pre-pubertal children at all. (We) ... urge clinicians to focus on diagnosis and then to seek proven treatments, rather than to engage in a simplistic and potentially risky symptom-ameliorating polypharmacy. (Ghaemi & Martin 2007)

However, the editorial did hold some sympathy with PBD researchers on the issue of psychiatric disorders possibly presenting differently in childhood.

4.8.6.3.2 Editorial and debate in the *Canadian J Psychiatry*

The Canadian Journal of Psychiatry ran a guest editorial (Smith DH 2007) accompanied by two lead articles with diametrically opposed views. The editorial was partly favourable to the PBD hypothesis but noted the intense controversy. The sceptical article, titled "Does bipolar disorder exist in children? A selected review", was by Anne Duffy whose research was funded by the Canadian Institutes of Health Research (CIHR) which is non-commercially funded, similar to the NIH in the US (Duffy 2007). Duffy focused on "studies of high-risk children of well-characterized parents with BD" and noted that bipolar disorder "most often debuts as a depressive episode in mid to late adolescence and that activated episodes are rare prior to age 12 years" (p. 409). Duffy's longitudinal high-risk offspring follow-up studies would later provide critical evidence regarding the way bipolar disorder develops (Chapter 4.8.7.2).

In stark contrast, Chang from California authored the other lead article titled "Adult bipolar disorder is continuous with pediatric bipolar disorder" (Chang 2007). Chang's disclosures listed the US NIH but additionally six pharmaceutical companies. He argued for a broad bipolar spectrum affecting up to 5% of the adult population and he quoted retrospective recall studies suggesting over 50% of adults with bipolar disorder have a childhood onset. However, retrospective studies are subject to recall bias, and divergent results reflect the perspective on bipolar disorder of both researchers and subjects (Post et al. 2008). Chang therefore acknowledged longitudinal studies were needed.

4.8.6.3.3 Editorial and debate over PBD in the *ANZJP*

A guest editorial in the *ANZJP* by two US PBD researchers suggested bipolar disorder was being missed in children and adolescents (Mao & Findling 2007). Fifteen child and adolescent psychiatrists including myself from South Australia wrote a letter to the editor indicating that PBD "is a controversial diagnosis" (p. 91) arguing that Australian and New Zealand psychiatrists needed to be aware of this debate (Parry et al. 2008; Appendix A1). Given the growing awareness of conflict of interest issues at that time, we referenced the contemporary article by Duffy in *The Canadian Journal of Psychiatry* and stated:

> Duffy's Canadian paper on the same issue comes to a rather different conclusion to the Mao and Findling paper. It is a sign of the times that readers increasingly look to disclosures when judging papers. Duffy discloses sponsorship from the Canadian Institutes of Health Research and no pharmaceutical company support. Mao and Findling list 21 pharmaceutical companies in their disclosures. (p. 91)

Another letter, from New South Wales, was also critical of PBD being presented in the *ANZJP* without an accompanying commentary (Parsonage & Hinds 2008):

> The views of Mao and Findling appear to accord with the practice of a number of Australian psychiatrists and we frequently see children graduating to our adult service who have been diagnosed with 'bipolar' and are on multiple medications, many of which cause potentially serious side-effects particularly weight gain, diabetes, and tardive dyskinesia. We are concerned that some of our colleagues seem so ready to diagnose BD in young people when the diagnosis is far from clear cut. (p. 92)

Parsonage and Hinds had witnessed a rise in PBD diagnoses during the mid-2000s. It seemed paediatricians and some child psychiatrists in New South Wales who had attended AACAP conferences and read the literature were applying the PBD diagnosing and treatment practices they had learned.

Additionally, a research group in New South Wales published in the *ANZJP* a review (Cahill, Hanstock, et al. 2007) comparing British NICE guidelines (NICE 2006) with the pre-pubertal PBD diagnostic guidelines from the US NIMH roundtable (Notelmann et al. 2001) and the US treatment guidelines in *JAACAP* (Kowatch et al. 2005). Cahill et al. advocated for a middle path between the US and UK diagnostic criteria: firstly, to have a lower threshold for diagnosis as per the NIMH recommendations, but a high level of observational follow-up for diagnosis confirmation as advocated in the British guidelines, and secondly, to take a more cautious approach to pharmacotherapy than the US treatment guidelines. They argued that the very conservative British NICE guidelines were too strict and would mean missing early and prodromal cases of bipolar disorder. However, the thorough and longitudinal research by the group eventually led to more conservative recommendations (Chapter 7.4.2).

4.8.6.4 **Book: *Pediatric Bipolar Disorder: A Global Perspective***

Adding to the emerging global perspective, a 2007 book explored the diagnosis (Diler 2007). Written from a pro-PBD viewpoint, the editor was described in Carlson's review of the book in JAMA (Carlson, 2009a) as follows:

> Rasim Diler, the editor of this volume, is originally from Turkey. He has been affiliated with the Western Psychiatric Institute in Pittsburgh, Pennsylvania, a hotbed of bipolar disorder research, for several years. (p. 2272)

Diler trained with, and later took a medical director role with, the Pittsburgh group led by Birmaher and Axelson. As an immigrant from Turkey he appeared passionate about international child psychiatry and the PBD hypothesis, as stated in the introduction:

> [A]vailable data suggest that prepubertal pediatric bipolar disorder is a highly comorbid, rapid cycling, mixed mood state and any data from around the world would definitely progress or even challenge our understanding … we have chapters from North America, Australia and NZ, Brazil and South America, China, Japan, India, Italy, Israel, Russia, Spain, and Turkey (p. x; italics in original).

Diler said the "book aims to take a snapshot of the current state of pediatric bipolar disorder in the world" (p. x; italics in original). The authors of each chapter were child psychiatrists from those countries or regions. Although most were sympathetic to the PBD hypothesis, the prevailing message was that it was viewed with majority scepticism in most countries. The relative exceptions were research teams in Turkey, Spain and Italy, where it was still acknowledged the diagnosis was controversial. Nonetheless hope was expressed in the book's foreword, written by Papolos, that "thankfully, the controversy has shifted from debate about whether it can be diagnosed to how it is diagnosed" (p. vii). Papolos concluded:

> The advent of a book that aims to give the field a first glimpse of the current state of knowledge about pediatric bipolar disorder from around the world, underscores the progress that has been made … and will hopefully encourage future efforts at international collaboration. (p. viii)

As indicated by the bibliometric research of international academic perspectives on a body of PBD literature (Parry, Allison, Bastiampillai 2019b; Appendix A35; Chapter 7), there had been little progress over the ensuing decade in such international collaboration.

4.8.6.5 **Parry & Allison (2008)**

Given the increasing awareness of PBD amongst psychiatrists and paediatricians in Australia and New Zealand at this time, Dr Steve Allison and I published a review in *Australasian Psychiatry* of the rise of PBD in the US and noted its controversial status (Parry & Allison 2008; Appendix A2). We presented an overview of the PBD hypothesis, its origins, the rapid translation into clinical practice in the US, and the controversy following the death of Rebecca Riley. We noted signs of uptake of the hypothesis in Italy, India and Brazil and queried whether PBD would "come to the Antipodes" (p. 83), but noted our soon-to-be published survey of the FCAP of the RANZCP indicated the "majority held to the traditional view that BD was rare before puberty and uncommon in adolescence" (p. 83).

4.8.6.6 **Dubicka, Carlson et al. (2008) trans-Atlantic comparison**

In this same year, Carlson co-authored with Bernadka Dubicka (Manchester University) a study of the divergent diagnostic practices of US versus British child psychiatrists (Dubicka et al. 2008). The US and British child psychiatrists viewed the same five clinical vignettes. There was close agreement on the vignette of an adolescent with classical manic features, but the US psychiatrists were significantly more likely to diagnose the other cases as bipolar disorder than their British colleagues. Published in the *European Journal of Child and Adolescent Psychiatry,* the authors speculated that the symptom checklist model of the DSM since DSM-III had influenced US child psychiatrists, whereas the British child psychiatrists were using a "pattern recognition" approach consistent with ICD-10 (p. 159). They also stated:

> The broadening of the concept of bipolar disorder with attendant consciousness raising in the US [12], has also been enhanced by aggressive marketing from drug companies with product indications for mania. This has probably contributed to an increased interest in reconceptualizing prepubertal children with serious behavior and mood regulation difficulties as having bipolar disorder. These marketing trends have not yet occurred to the same extent in the UK and thus may partly explain the reduced recognition of the disorder found in this study. (p. 160)

These speculative comments received evidentiary support contained in subpoenaed pharmaceutical company documents released from court cases over the next few years (Chapter 4.2).

4.8.6.7 **Post et al. (2008) *British J Psychiatry***

Further illustrating the marked trans-Atlantic discrepancies, Professor Robert Post (George Washington University) and colleagues from the US, the Netherlands and Germany, published an interesting study of retrospective recall by adults (mean age 42) with bipolar disorder, as to when their first depressive or hypomanic/manic episode occurred. The difference was striking: "Only 2% of patients had childhood-onset bipolar disorder across the three European sites, compared with 22% in the four US sites" (p. 150) (Figure 4.27) and "61% of the US patients had their onset of bipolar disorder prior to age 19 years - double the rate for the European sites (30%)" (p. 151).

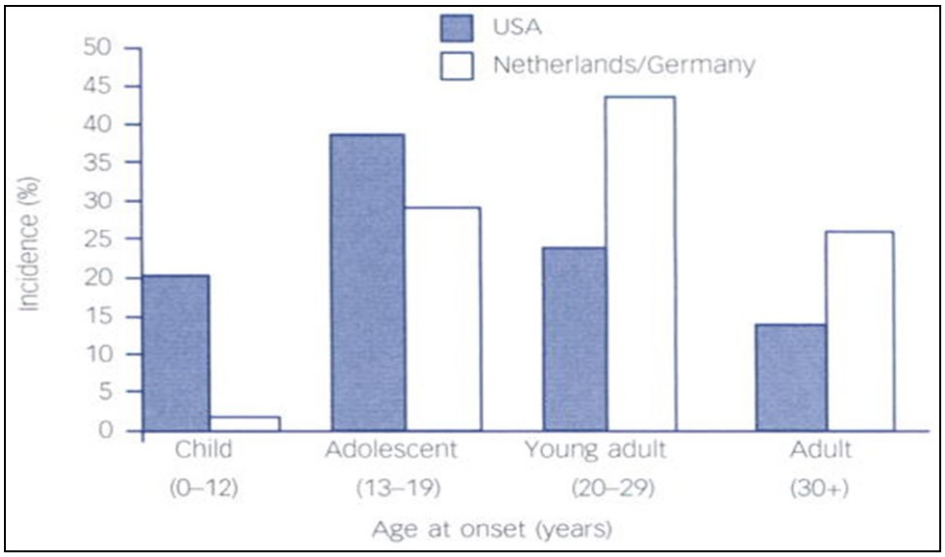

Figure 4.27: Age at onset bipolar disorder: comparison of US and European samples (Post et al. 2008, p. 150). Reproduced with permission.

The US cohort of adults had greater rates of rapid-cycling dysphoric mania, histories of child abuse, depressive episodes, suicide attempts and substance use disorders. This suggests some of these patients would possibly have been diagnosed instead with a personality disorder in European clinics. However, Post et al. speculated on mechanisms that may have led to a greater genetic vulnerability of US residents to bipolar disorder or increased environmental factors in the US including childhood adversity, diet, environmental toxins and stimulant medication for ADHD.

The German and Dutch adults' recall rate matched that of an Australian study published the previous year.

4.8.6.8 **Berk et al. The Australian BCOS study, 2007**

The Bipolar Comprehensive Outcomes Study (BCOS) was a 2-year prospective study of Australian adults (mean age 41.8 years) with Bipolar I or Schizoaffective disorder (Berk et al. 2007). The study asked 218 subjects to recall their lifetime history of psychiatric symptoms. While delay from early symptoms to psychiatric treatment was lengthy, the median age of onset of actual manic symptoms was 21-years-old and of a diagnosable manic episode was 24.1-years-old (Figure 4.28). These recollections of middle-aged adults accord with the data collected by Kraepelin from his adult patients a century earlier (Chapter 2.1). The lengthy delay to treatment, however, stresses the need for service provision in child, adolescent and young adult mental health, particularly for high-risk offspring of parents with classical bipolar disorder and psychotic spectrum disorders.

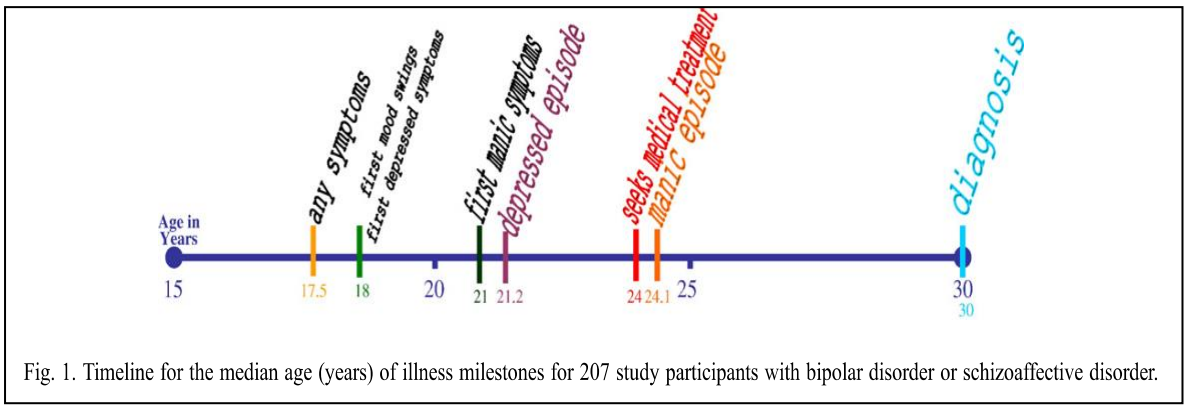

Fig. 1. Timeline for the median age (years) of illness milestones for 207 study participants with bipolar disorder or schizoaffective disorder.

Figure 4.28: Timeline for the median age (years) of illness milestone for 207 study participants with bipolar disorder or schizoaffective disorder (Berk et al. 2007, p. 183)

Reproduced with permission.

4.8.6.9 **Carlson (2011) *British J Psychiatry***

Based on an evident marked divergence of international opinion, between the US on one hand, and Europe, Australasia and Canada on the other, Carlson called for further research. In an article in the *British Journal of Psychiatry* titled "Will the child with mania please stand up?" she appealed for a "study similar to the cross-national International Pilot Study of Schizophrenia, launched 50 years ago because of very different rates of schizophrenia and manic depression found in the US compared with the UK" in order to "emerge from" the PBD controversy (Carlson 2011, p. 172).

4.8.6.10 **Chan et al. (2011) *CAMH* British NHS paediatric rates**

Seemingly immediately meeting Carlson's call, and illustrating the trans-Atlantic divide, Chan and colleagues reviewed the inpatient and outpatient ADHD and bipolar disorder diagnoses from a large English Child and Adolescent Mental Health Service, involving 3,586 children and adolescents presenting over a 15-year period from 1992 to 2007 (Chan, Stringaris & Ford 2011). There were 341 cases of ADHD, 35 cases of bipolar disorder and only two cases (boys aged 7 and 11) who had co-morbid bipolar disorder and ADHD. The mean age for ADHD was 8.7-years (SD ±3.07) and for bipolar disorder was 14.3-years (SD ±2.16). The ADHD cases had generally been symptomatic for over a year, the bipolar cases generally for less than six months. ADHD cases were 85% male, the bipolar cases 51% male. The ADHD cases were associated with neurodevelopmental delays, while the bipolar disorder cases were not but had significant depression and suicidality. Only 9 cases (0.3%) of bipolar disorder under age 13 and two-thirds were girls. Exact ages were not given.

In other words, the UK Child and Adolescent Mental Health Service was not diagnosing PBD but traditional bipolar disorder. Given this was a large clinical sample over a lengthy time frame involving both an outpatient service and an inpatient unit with a large catchment, the findings indicated pre-pubertal bipolar disorder diagnosis in the UK to be exceedingly rare.

4.8.6.11 **FCAP of RANZCP survey on PBD, published 2009**

As mentioned above, during late 2007 Stephen Allison, Gareth Furber, and I conducted a survey of members of the FCAP of the RANZCP. This was initially published in the *Bulletin of the Faculty of Child & Adolescent Psychiatry* (Parry, Allison & Furber 2008; Appendix A5) from which Figure 4.29 is taken. The bar chart represents responses to the question: "In your opinion, PBD is overall: somewhat underdiagnosed; appropriately diagnosed; somewhat overdiagnosed; very overdiagnosed; or unsure." A longer peer-reviewed article was published in *Child and Adolescent Mental Health* (Parry, Furber & Allison 2009a; Appendix A4). There was a 60% response rate from the faculty, amounting to 199 responses. We concluded:

> This paper reports on a survey of Australian and New Zealand child and adolescent psychiatrists and finds a solid majority retain a traditional view of bipolar disorder and are sceptical of the new PBD phenotypes. (p. 140)

Key findings included: 51% thought the prevalence of pre-pubertal bipolar disorder was “very rare (<0.01%), 30% thought it “rare (<0.1%)”, 16% thought it “uncommon (0.1-0.5%)”; one person (0.5%) thought it “common (0.5-3%)”; no-one thought it “very common (3 to 5% or more)”, but only 2% thought bipolar disorder could not be diagnosed prior to puberty (pp. 143-144).

In terms of seeing cases themselves: 53% had never seen a pre-pubertal case in their careers (mean career 15 years); 29% had seen “1 or 2” cases; 8% had seen “3 to 5” cases; 3% had seen “6 to 10” cases; 5% had seen “11 to 15” cases; 2% had seen “>15” cases. Thus, whilst a large majority of Australian and New Zealand child and adolescent psychiatrists held the classical view that bipolar disorder was very rare prior to puberty, a small minority had by 2007 adopted the PBD hypothesis.

Furthermore, there was a consensus that PBD was “over-diagnosed” in the US (Figure 4.29). Eighty-four percent of Australian and New Zealand child psychiatrists thought “other diagnoses, e.g.: ADHD, adjustment disorders, PTSD, parent-child problems, peer relationship problems – probably explain many of the cases of PBD in the USA”; only 3.5% disagreed with this proposition; the remainder were “neutral” or “unsure” (p. 144).

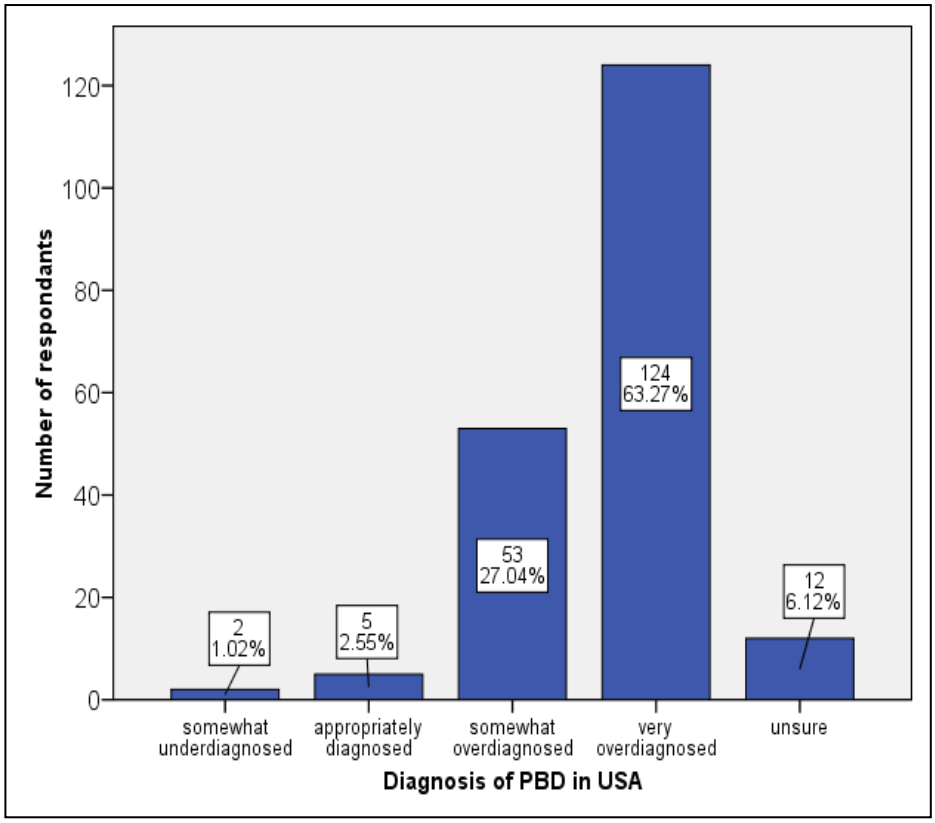

Figure 4.29: "In your opinion, PBD in the USA at present is overall…" (Parry, Furber & Allison 2008, p. 8)

However, it was not all one way. Opinions were split as to whether bipolar disorder in the paediatric age range was over-diagnosed (25%), appropriately diagnosed (42%) or under-diagnosed (28%) in Australia and New Zealand (p. 144).

A minority of participants gave optional comments. While not submitted to *Child and Adolescent Mental Health*, the comments (fully listed in Appendix A7) provided qualitative depth and were summarised in the *Bulletin of the Faculty of Child & Adolescent Psychiatry (RANZCP)* (Parry, Allison & Furber 2008; Appendix A5).

The survey was conducted at what historically appeared to have been the peak of the PBD diagnostic wave in Australia and New Zealand. It was noted that paediatricians, particularly in New South Wales, were a group likely to diagnose PBD in pre-pubertal children. Recent informal discussions suggest that if the survey were re-run now, a decade later, results would likely reflect a more sceptical perspective.

4.8.6.12 **Swedish 15-year follow up of adolescents with "hypomania"**

In 2013, a Swedish 15-year follow up study of adolescents with depression and hypomania, cast significant doubt on the long-term significance of adolescent hypomania (Päären et al. 2013). The findings were unexpected and dramatic: 94% of adolescents with hypomania did not have hypomanic recurrences in adulthood and only 3% had developed mania. The original community high school sample consisted of two thousand three hundred 16 – 17-year-olds. Of 90 adolescents who reported lifetime hypomanic syndromes, 64 cases (71%) participated in follow-up at age 31 – 33-years-old. Of these, 38 adults (59%) reported an adult major depressive episode, only four (6%) reported recurrence of hypomania and only two (3%) reported a manic episode. Other features of the cohort suggested that this result was not due to the 26 cases lost to follow up.

If so few cases of adolescent hypomania progress to bipolar disorder by their early 30s, it suggests it is premature to give a lifetime bipolar disorder diagnosis to adolescents with hypomanic features. This Swedish data is similar to Cicero, Epler and Sher (2009)'s finding that high youth rates of mania and hypomania did not proceed into later life.

In a second paper further analysing the same data, the authors stated:

> Somewhat surprisingly … adolescents with hypomania spectrum episodes did not have a higher risk of BPD in adulthood compared with those with only MDD. (Paaren et al., 2014, p. 2)

However, they did have similar levels of non-bipolar adult psychopathology to adolescents who had experienced MDD. The data for the 6% with adult recurrences suggested that having psychotic symptoms or a family history of Bipolar-I or Bipolar-II disorder was associated with increased risk of adult hypomania/mania. In a further surprise, whether the baseline hypomania was full or subsyndromal was found to be not significant.

These findings of potential risk factors for true bipolar disorder corroborate the conclusions of the Canadian, Danish and US Amish offspring studies, which have been reported in recent years (Chapter 4.8.7 below).

4.8.6.13 **Comparison of US and English hospital PBD diagnosis rates**

James and colleagues from Oxford University co-authored with Leibenluft of the NIMH an 11-year comparison of English with US discharge diagnosis rates for bipolar disorder in 0 – 19-year-olds, as well as 20 – 34-year-olds, from 1 January 2000 to 31 December 2010 (James et al. 2014). The dataset was comprehensive in England, including all NHS hospital discharges. In the US, data for 500 hospitals from 2000-2007 and 239 hospitals from 2008-2010 were used. The study was published in *JAACAP.* The results, as shown in Figure 4.30 and Figure 4.31 revealed a stark contrast:

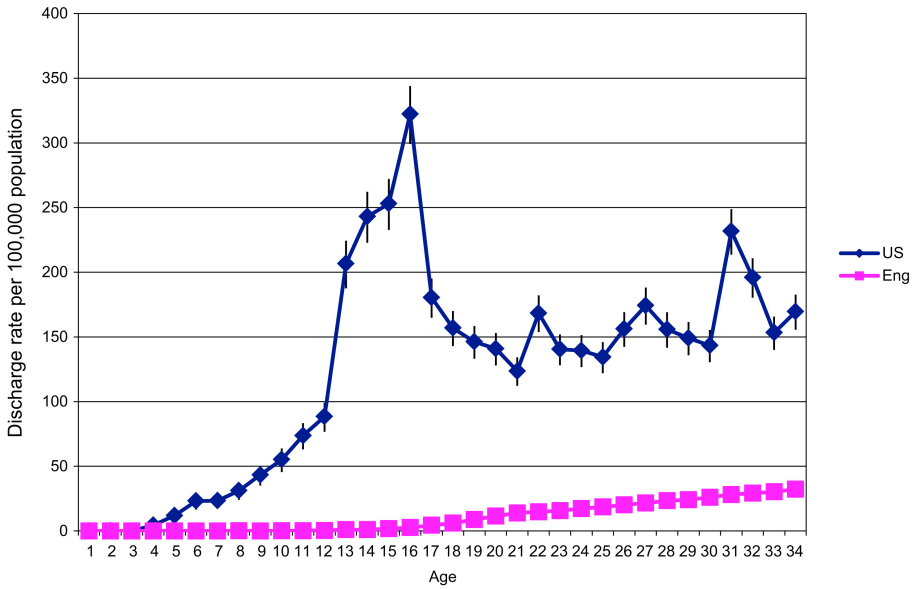

Figure 4.30: Bipolar disorder (BD) (ICD-9-CM codes 296.40-296.89; ICD-10 code F31) discharge rates per 100,000 population in patients aged 1 to 34 years in the United States versus England, 2000 to 2010 (James et al. 2014, p. 618). Reproduced with permission.

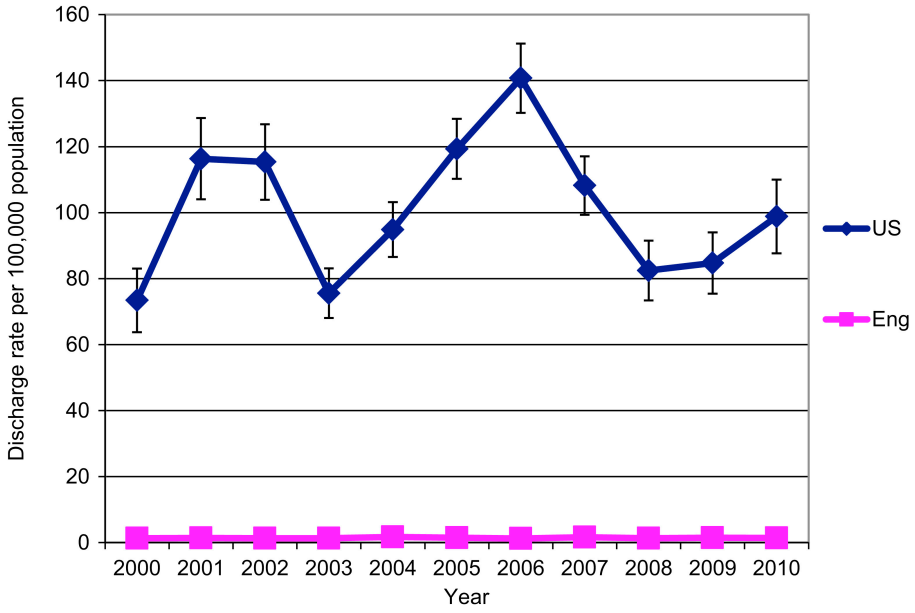

Figure 4.31: Pediatric bipolar disorder (PBD) (ICD-9-CM codes 296.40-296.89; ICD-10 code F31 in patients aged 0-19 years) discharge rates per 100,000 population in the United States versus England by year, 2000 to 2010 (James et al., 2014, p. 619). Reproduced with permission.

The disparities between the US and England for full bipolar spectrum diagnoses were:

- 72.1-fold for the full under-20 age range
- 114-fold difference at age 16-years when diagnoses peaked in the US
- not calculable for preadolescent ages as there were no diagnoses in England; more diagnoses were made in the US by age 5 than by age 19 in England.

For each specific bipolar diagnosis, the disparities in the under-20 age range were:

- 56.7-fold for Bipolar-I
- 570-fold for Bipolar-II, 73.7-fold for BD-NOS
- 40-fold for cyclothymia.

The disparity for adults was 7.2-fold. For other non-bipolar mental disorders, the disparity was 3.9-fold, with ADHD high at 13.2-fold.

The authors noted that the lengths of stay were considerably longer in England, and readmissions of patients in the US may have boosted the rate there, but even if length of stay was factored in, the discrepancy for the under-20 age range was still 12.5-fold. They speculated, that “viewing irritability, not euphoria, as the hallmark symptom of pediatric

mania" may be a main factor in the discrepancy, and that such cases in the UK "would be conceptualised not as PBD but as oppositional defiant disorder, conduct disorder and/or ADHD with emotional dysregulation" and cited the trans-Atlantic clinical vignette diagnostic study of Dubicka et al., (2008) as confirmation (p. 621).

4.8.6.13.1 *JAACAP* editorial and letters debate re James et al. (2014)

The accompanying editorial in *JAACAP,* "Unpacking the differences in US/UK rates of clinical diagnoses of early-onset bipolar disorder", suggested the disparity reflected "administrative" (i.e. diagnostic process) rather than "epidemiologic" prevalence (i.e. "true" prevalence) (Stringaris & Youngstrom, 2014a, p. 609). The authors, Stringaris (Kings College London) and Youngstrom (University of North Carolina), referred to the oft-cited meta-analysis of 12 community epidemiological studies by Youngstrom and colleagues (Van Meter, Moreira & Youngstrom 2011). for what they called the "true prevalence" rate that "does not vary between countries" (p. 609).

They agreed that diagnosis rates were elevated in the US by interpreting chronic irritability as PBD, and that there were diagnostic up-coding forces due to managed care. Yet referring to low ADHD diagnosis rates in the UK, and to a "minority of UK clinicians' … surprising" denial of pre-pubertal bipolar disorder, they stated: "An alternative explanation could be that appropriate awareness of the disorder has increased in the United States compared with the United Kingdom." (p. 609). They did not mention the other possibility, namely: that an appropriate level of awareness of the disorder had continued in the UK.

In response, Louise Richards, British child psychiatrist, and myself submitted a letter to *JAACAP* (Parry & Richards 2014; Appendix A27), which incorporated data from the previous five years of discharge diagnoses from the under-14 age inpatient unit in Brisbane:

> Of 505 patients (3-15 years old, mean 9.8 years) admitted over 5 years, from July 1, 2009 to July 1, 2014 only two had ICD-10 F31 bipolar spectrum diagnoses: a 14-year-old boy with F31.3 (bipolar disorder: mild-moderate depression) and a 14-year-old girl with F31.6 (bipolar disorder: mixed). In addition, there was a 14-year-old girl with code F25.2 (schizoaffective disorder: mixed type), a 13-year-old girl with F25.9 (schizoaffective disorder: unspecified), and 15 youth (12-14 years old)

> with code F20 (other psychotic disorders). The unit's catchment is most of Queensland, whose population is 4.67 million people. (p. 1234)

The lack of pre-pubertal cases of bipolar disorder in Australia's third largest state was similar to the English findings of James et al. (2014).

Richards and I critiqued the assertion that the Van Meter et al. (2011) meta-analysis of epidemiological studies was more likely to provide a "true" prevalence than diagnoses by clinicians and noted the scepticism regarding PBD among Australasian and British child psychiatrists as evidenced in the FCAP of RANZCP survey (Parry, Furber & Allison 2009a) and a 2010 British FCAP of RCPsych conference debate on the issue.

Stringaris and Youngstrom replied to our letter (Stringaris and Youngstrom, 2014b). Amongst other points, they stated:

> The authors use as an argument against "US PBD phenotypes" the fact that other countries do not recognize them. This is a rather weak argument, because it implies that for some reason, the United Kingdom, Australia, or New Zealand are somehow intrinsically psychiatrically superior. Such a statement can easily be interpreted as snobbery … the authors suggest that a vote and a committee's decision should swing us all to becoming BD deniers. This should, of course, be rejected outright, because scientific matters ought to be decided by science rather than by majority decision or decree (p. 1235).

This was an extraordinary statement: it is worth pointing out here that the British NICE guidelines are an example of deciding scientific matters by an expert committee, evaluating the scientific evidence, and, unlike for example the PBD treatment guidelines work group in the US (Kowatch et al. 2005), NICE is completely free of commercial sponsorship. NICE is to the UK something akin to the NIMH in the US, therefore it is somewhat strange that it did not seem to be afforded a similar level of respect in this *JAACAP* editorial.

4.8.6.14 **Further international bipolar disorder discharge rates**

4.8.6.14.1 **All Danish bipolar diagnoses for under-19 years old, 1995 to 2012**

Kessing et al. (2014) reported on all inpatient and outpatient diagnoses of 18-year-olds and younger with bipolar disorder in Denmark from 1 January 1995 to 31 December 2012. They

noted the high rates in the US. Their article preceded that of James et al. and they stated that: "no study outside the USA has been published on the rates of clinical pediatric bipolar disorder" (p. 1).

Danish data records meant all bipolar disorder diagnoses were collated. Total diagnoses for the full 18 years amounted to 346 cases. There was an increase in the second eight-year period (235 cases for 2004-2012) compared with the first period (111 cases for 1995-2003): the authors hypothesised that in the first period more diagnoses (70.3%) were made during an acute manic episode, while in the second period less diagnoses (48.3%) were made during acute mania (p. 6). The other diagnoses made during remission may have gathered more Bipolar-II cases previously missed. Given a Danish under-19 population of 1,175,201, the authors reported the annual incidence of bipolar disorder was 0.001% in the earlier part of the study period and 0.004% by the end.

Regarding age of onset the authors found:

> [M]edian age at the index diagnosis was rather high (17.2 years) and that only 25% of the patients were below 16.2 years of age when the diagnosis of mania/bipolar disorder was made for the first time, reflecting that child bipolar disorders are rarely diagnosed in Denmark. (p. 6)

These findings from a nation that by world standards has excellent data collecting capability, support the classical perspective of hypomania/mania as condition that onsets in late adolescence, and generally not in prepubertal childhood.

4.8.6.14.2 Clacey et al. (2015) five nations comparison

In 2015, the Oxford group added to their US and England comparison with a study that incorporated hospital discharge diagnosis rates from Germany, Australia and NZ (Clacey, Goldacre & James 2015). Rates for the full spectrum of bipolar disorders were markedly higher in the US than the other four nations for the under-20 age group. The greatest discrepancy was in the pre-adolescent group:

> In the 5-9 age group, the US rate was 27 per 100 000, whereas all other countries had rates of less than 1 per 100 000 (Australia 0.14, New Zealand 0.22, England 0.00 and Germany 0.03). In the 10-14 age group, the US rate was 134 per 100 000,

whereas all other countries had rates of less than 5 (Australia 3.9, New Zealand 1.3, England 0.48 and Germany 0.46). (p. 167)

Figure 4.32 illustrates these statistics.

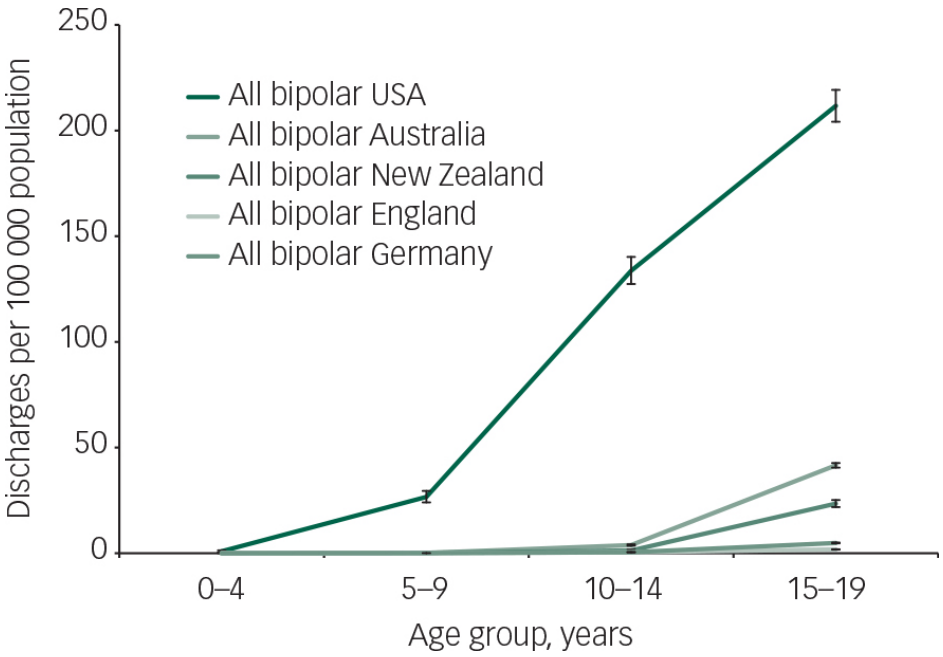

Figure 4.32: All bipolar disorder discharges per 100 000 population for patients aged 0-84 in the USA, Australia, New Zealand, England and Germany, 2000-2010 (Clacey, Goldacre & James 2015, p. 168). Reproduced with permission.

There was much less variation with other discharge diagnoses. In the US, the rate of ADHD was modestly higher and unipolar depression only marginally higher. Extended length of stay for inpatients and fewer actual admissions contributed to English discharge diagnosis rates being lower than other nations for all disorders.

The rate of bipolar disorder diagnoses in patients age 50-years and older was roughly comparable between the US and the other four nations. As discussed in Chapter 1.2, there have been concerns about over-diagnosis of bipolar disorder in adults. Studies have suggested over-diagnosis in adults has been a greater problem in the US, but it is an issue in Europe and Australasia as well. It is the PBD hypothesis that has not been adopted internationally, whereas to some extent the adult soft bipolar spectrum hypothesis has.

Notably however, the rate of "borderline/emotionally unstable personality disorder" was considerably lower in the US than all four other nations. Summing up, Clacey et al. attributed these findings to, differing concepts of diagnosis in US psychiatry; US diagnostic up-coding pressures; and that:

> [T]here have also been concerns expressed that trauma, attachment and other psychosocial factors are not properly considered when looking to make diagnoses in young people with affective instability (Parry & Levin, 2012). (p. 171)

This observation is relevant to the familial studies in PBD research and the Pittsburgh offspring study, where PBD children are described as having strong family histories of bipolar disorder. It is also reflective of the retrospective recall study of age of onset by comparing US with German and Dutch adults with bipolar disorder (Post et al. 2008). These findings suggest that what would be diagnosed in other jurisdictions as personality disorders, suggested by familial comorbidities with externalising disorders and psychosocial problems, are more likely to be diagnosed with bipolar disorder in the US. If this is indeed the case, as noted by Carlson and Klein (2014), then this would be a confounding factor in the pro-PBD hypothesis versus classical perspective familial and genetic research literature.

4.8.6.14.3 Goetz et al. (2015) Czech inpatient study

A similar 2015 publication on discharge diagnostic rates of bipolar disorder in children and adolescents under age 18 came from the Czech Republic (Goetz et al. 2015). This Czech study was a thorough analysis of the phenomenology, age of onset and course of illness and family history of 46 patients diagnosed with DSM-IV bipolar disorder (93% Bipolar-I, 7% Bipolar-II) from two child and adolescent psychiatric units in Prague from 1997 to 2014. During that period there had been 5,483 individual patients admitted, therefore the discharge diagnosis rate was 0.83%, a figure close to the European and Australasian statistics. The authors noted German (Holtmann et al. 2010), Danish (Thomsen et al. 1992) and Finnish (Sourander 2004) studies as being comparable, and in citing Blader and Carlson (2007), commented: "Differences among European countries are notably smaller than differences between Europe and the US." (p. 2856).

Some key findings from Goetz et al. included:

- a roughly equal gender split
- phenomenology was of classical manic and major depressive/sometimes melancholic symptoms
- often other diagnoses were made before it became clear the child/adolescent was suffering from bipolar disorder
- 56% of first mood episodes were depressive, 24% were hypomanic and 20% were mixed
- manic episodes were an average of two years after the initial mood episode; the youngest first manic episode was at age 11.5-years-old
- the mean age of first manic episode was 15.6 years of age, and
- very-early-onset (<13 years old) (n =7) cases were more likely to have suffered trauma and have a parent with bipolar disorder than early-onset (> age 13 years) cases (n=39).

In their discussion, Goetz and colleagues noted the COBY study from Pittsburgh but that their findings were at odds with this:

> Birmaher et al. in a study of high-risk offspring found hypo/mania in 9.7% of children with bipolar disorder less than 12 years of age and the diagnosis of BD not otherwise specified was established in 46% of children with bipolar disorder before they reached 12 years of age (Birmaher et al., 2009). Our current data correspond with the more classic view. (p. 2861)

These Czech Republic figures coincided with the other European and Australasian diagnostic data. Based on classical concept of mania, only exceedingly rare pre-adolescent cases were being diagnosed.

4.8.6.14.4 Rao et al. (2016) German inpatient update study

In Germany Rao and colleagues updated the "hospitalisation rates for specific psychiatric disorders" for the period of 2008 to 2013, building on the trends described by Holtmann et al. (2010) for the period 2000 to 2007 (Rao et al. 2016, p. 1). They found that the rate per 100,000 of population of discharge diagnoses of ICD-10 F31 code bipolar disorder increased in the under-15 age group from 0.14 in 2000 to 0.3 in 2013, and the rate for the 15 – 19-year-old group from 3.85 to 8.14 over the same time. However, there was an increase in psychiatric

inpatient beds during that period, and the rate of other psychiatric disorders, particularly depressive disorders, increased as well, though the psychotic disorders rate fell (Figure 4.33).

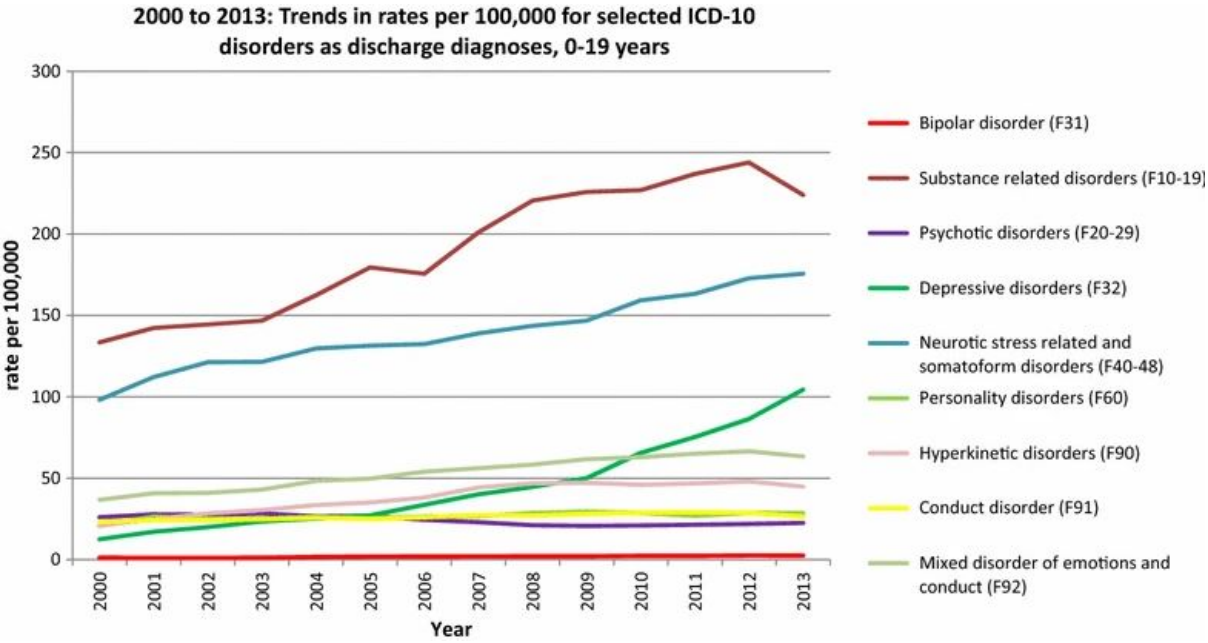

Figure 4.33: Trends in the rates (per 100,000) of BD as a discharge diagnosis, by age group, from 2000 to 2013 (Rao et al. 2016, p. 4). Reproduced with permission.

As can be seen the rate of bipolar disorder diagnoses remained a very small fraction of all psychiatric admissions of children and adolescents in Germany, varying from 0.22% to 0.27% of *psychiatric admissions* (*not* population prevalence), during the time period.

In summary, recent inpatient diagnosis studies covering all child and adolescent psychiatric inpatients from England, Germany, Australia, NZ, and the Czech Republic, as well as a Danish study of all inpatients and outpatients under age 19 bipolar disorder diagnoses, all gave findings in line with the classical perspective. These are consistent with the clinical cohort prevalence from Denmark, Finland, the UK and NZ that predate the PBD hypothesis (Chapter 2.4). The classical perspective has continued in much of Europe and Australasia.

4.8.6.15 **Post et al. (2017) hypothesise pre-pubertal PBD truly higher in US**

Also investigating European-US comparison studies, Post and colleagues built on their earlier study (Post et al. 2008; Chapter 4.8.6.7). They reviewed recent literature, including offspring

and discharge diagnosis studies (Post et al. 2017). In regard to the US-UK diagnosis figures of James et al. (2014) they stated:

> The rate of 100.9 hospitalizations per 100,000 population for childhood onset bipolar disorder in the US compared to 1.4/100,000 in England is astounding. That represents a lot of very sick children being hospitalized in the US even if there are some ambiguities about the diagnostic labelling. (p. 209)

However, to explain these "very sick children", they mostly discounted the over-diagnosis hypothesis, but as in their 2008 paper, suggested, the "US has more genetic/familial risk factors for childhood onset bipolar disorder than the Europeans"; more environmental stressors (both toxins and social adversity) (p. 208); and increasing diagnoses in the US may represent epigenetic changes for the worse (p. 209).

They acknowledged that more intervention was needed in the US to address "verbal, physical, and sexual abuse or neglect" and that "family focused therapy" had shown promise for PBD diagnosed youth, whereas a study by Findling et al. (2007) found that divalproex sodium had "no significant effect" (p. 210). This recognition of the need to research and intervene for family dynamic, attachment and maltreatment and trauma factors is a welcome development that, if truly implemented, should reduce the number of 'very sick children' in the US.

4.8.7 **Longitudinal prospective studies of bipolar offspring**

4.8.7.1 **Canadian offspring study comes to fruition**

In 2014, Duffy and colleagues from several Canadian institutions published their findings of a 16-year longitudinal study of 229 high-risk offspring from 113 families, where one parent had a Bipolar-I diagnosis (Duffy et al. 2014). There were 86 control offspring from 55 families. Diagnosis procedures were annual:

> All offspring were assessed by a psychiatrist masked to family affiliation at baseline and subsequently annually (on average) or anytime symptoms developed using the Kiddie Schedule for Affective Disorders and Schizophrenia – present and lifetime version (KSADS-PL)/ SADS-L format interviews (depending on their age). DSM-IV diagnoses were based on best estimate procedures using all available

> clinical information and reviewed on a consensus basis by two additional research psychiatrists masked to family affiliation. (p. 123)

Thirty-one of the 229 (13.54%) of the high-risk offspring had by this time been diagnosed with a bipolar spectrum disorder (Bipolar I, Bipolar II, Bipolar NOS, Schizoaffective disorder). There was one diagnosis of Cyclothymia. The breakdown figures were by cumulative lifetime diagnosis and added up to 22.21% of the offspring cohort: (Bipolar-I = 3.41%, Bipolar-II = 6.24%, Bipolar-NOS = 7.29%, Schizoaffective disorder = 4.79%, Cyclothymia = 0.47%).

Offspring group results discriminated starkly from the control group. There were zero bipolar spectrum diagnoses in the control cohort. There were two cases of MDD, one of Depression-NOS and twice as many Adjustment disorder cases than among the offspring.

Key findings for the offspring developing bipolar spectrum disorders were the age of onset and prodromal symptoms and syndromes. The index (i.e. first) mood episode in 84% of cases was depressive:

> There was no case of diagnosable mania or hypomania observed prior to age 15.5 years, and the earliest at which an offspring met the DSM diagnosis for bipolar disorder NOS was 12.5 years. (p. 125)

The average age of first (hypo)manic episode in those whose index episode was depressive was 20.85-years (SD ±4.82). The age of onset was on average two years earlier in offspring whose parents were lithium non-responders and all cases of schizoaffective disorder had parents who were lithium non-responders.

Offspring who went on to develop bipolar disorder were much more likely to have sleep disorders than control offspring, and twice as likely to have anxiety disorders and substance use disorders. Their anxiety disorders had an earlier age of onset (median age 8.76 compared with 12.74-years for controls). Offspring of parents whose bipolar disorder illnesses were not responsive to lithium were more likely to have neurodevelopmental disorders, akin to the childhood history for schizophrenia, but those whose parents were lithium responsive were not. This suggests a biological distinction between classical bipolar disorder and the schizoaffective part of the psychotic spectrum of disorders, despite likely overlapping genes.

4.8.7.2 **Proposed clinical staging for development of bipolar disorder**

Based on these findings, and from other offspring studies (see below), Duffy et al. proposed a staging model for bipolar spectrum disorder in their 2014 report on the Canadian offspring study. Duffy elaborated further on this staging model the following year (Duffy 2015), with a figure providing graphic illustration of the progression to illness, reproduced here as Figure 4.34. She described the staging model as follows:

- Stage 0 (well, but at confirmed familial risk given a first-degree affected relative)
- Stage 1 (in those at familial risk — non-mood childhood disorders including sleep and anxiety disorders, and in some children cognitive deficits/ADHD)
- Stage 2 (in those at familial risk – minor mood, single episode depression and adjustment disorders such as anxiety and mood symptoms in association with a stressor around puberty)
- Stage 3 (recurrent major depressive disorders typically in mid-to-late adolescence)
- Stage 4 (bipolar or schizoaffective disorder typically late adolescence to early adulthood). (pp. 7-8)

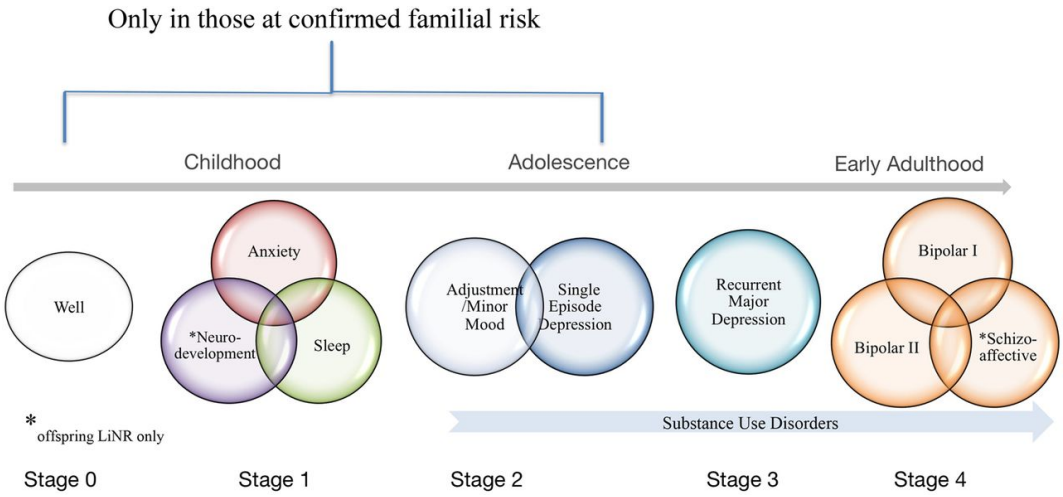

Figure 4.34: Developmental clinical staging model of bipolar disorder (Duffy 2015, p. 8). Reproduced with permission.

This prospective long-term Canadian offspring study was providing a potentially accurate developmental map for early detection and intervention for young people at high risk of

classical bipolar disorder or schizoaffective disorder. The findings though are at odds with the PBD hypothesis of brief manic episodes and high disruptive behaviour disorder comorbidity.

4.8.7.3 **Duffy & Malhi (2017) *ANZJP* editorial**

Malhi also co-authored an *ANZJP* editorial with Duffy on the subject of prospective longitudinal bipolar offspring studies (Duffy and Malhi, 2017). They critiqued the PBD phenotypes for being "strikingly different" to the early course of bipolar disorder as identified as developing in "familial high-risk populations" (p. 761). Summarising the findings from offspring studies, Duffy and Malhi noted:

1. "mania (using adult criteria) is rare prior to puberty", even in high-risk families
2. the onset is usually with depressive episodes in "mid-adolescence" that are "indistinguishable from unipolar depression"
3. "childhood antecedents include sleep, anxiety and sub-affective disorders" which are subject to variability and only presage possible bipolar disorder where there is strong genetic risk (p. 761).

As had Malhi's articles in *The Lancet* and *Bipolar Disorders*, they critiqued the quest for early identification and intervention based on soft possible early signs of bipolar disorder in youth when they concluded:

> Thus, although we broadly support the concept of mapping illness trajectories with a view to ultimately staging bipolar disorder, we feel that the field as a whole, and in particular researchers targeting bipolar disorder, should take careful aim before 'firing' and that much more reconnaissance is needed in order to fully appreciate the bipolar landscape. (p. 763)

In a letter titled "Paediatric bipolar disorder: Reality or myth?" (Parry, Allison & Bastiampillai, 2018c; Appendix A30) responding to Duffy and Malhi's (2017) editorial, we drew attention to our review of the epidemiological surveys (Parry, Allison & Bastiampillai 2018a). We noted that "the methodologically best study" (Stringaris, Santosh, et al. 2010) "authors commented that bipolar-NOS appeared unrelated to bipolar-I or bipolar-II" and were recommending the use of the term 'mood lability' as "more appropriate" (p. 901) and consequently we suggested:

> Based on the best evidence from the bipolar offspring studies and the child and youth epidemiologic surveys, it would be preferable to dispense with the term 'PBD' at this stage. (p. 901)

Our point was that the term 'bipolar disorder' needs to apply to a condition with valid episodes of hypomania/mania in concert with DSM and ICD definitions. Evidence from these longitudinal studies supported the classical perspective of late adolescent and older onset and that 'PBD' was often describing mood lability and behaviour dysregulation in younger children that in most cases was unrelated to true bipolar disorder.

4.8.7.4 **Pfennig et al. (2017) *ANZJP* review of prospective studies**

Duffy and Malhi had also extensively quoted a review of 19 prospective studies examining the psychopathology of early onset bipolar disorder, published in the *ANZJP* three months earlier (Pfennig et al., 2017). The 19 studies included the Pittsburgh BIOS study. Pfennig and colleagues noted:

> [I]t is important to consider that using bipolar spectrum disorder (as opposed to full bipolar disorder) … mixes predictors with outcome since bipolar spectrum symptoms are found as predictors of full disorder … it should be acknowledged that some of the risk factors might be non-specific risk factors of adult mood disorder, not only of bipolar disorder … The time of puberty and adolescence is frequently marked by strong emotional and social developmental changes so that the differentiation between healthy and pathological features is even more difficult (p. 520).

Thus Pfennig et al. were implicitly criticising the PBD hypothesis for over-diagnosing non-specific symptomatology that may or may not be harbingers of bipolar disorder, for the real disorder itself.

4.8.7.5 **Duffy et al. (2017b) summary findings from offspring studies.**

In an important review, that would bring some firm international data to solve the PBD hypothesis controversy, Duffy collaborated with the Swiss longitudinal study group, led by Professor Martin Preisig (University Hospital of Lausanne), in a narrative review covering the gamut of findings from six key prospective longitudinal studies of the high-risk offspring of bipolar parents and related meta-analyses (Duffy et al., 2017b). The data revealed the

symptomatology that characterised the early development of bipolar disorder. The nationality of each of the six offspring studies it reviewed are:

- Canadian (Duffy et al., 1998, Duffy et al., 2014)
- Dutch (Wals et al., 2001, Mesman et al., 2013),
- US Amish (Egeland et al., 2003, Egeland et al., 2012),
- US multisite University of Indiana (Nurnberger et al., 2011),
- US Pittsburgh "BIOS" (Birmaher et al., 2009, Axelson et al., 2015), and
- Swiss (Preisig et al., 2016, Vandeleur et al., 2014).

This was the most comprehensive review of longitudinal offspring studies to date, and the findings are summarised here in depth:

- The PBD hypothesis as mostly promulgated over the past 20 years or so is incorrect: instead:
    - [M]anic-like presentations in very young children without a confirmed family history of bipolar disorder may index a set of disorders or problems unrelated to bipolar disorder. (p. 6)
- While the PBD hypothesis, in all its phenotype manifestations, claimed extremely high comorbidity with ADHD and other disruptive behaviour disorders, Duffy et al. found that:
    - ADHD and behavioural disorders are not consistently elevated in high-risk offspring after adjustment for family factors … and bipolar subtype (psychotic spectrum illness) (p. 2)
- True bipolar disorder is a highly heritable condition: "a first degree relative of a bipolar patient has an estimated eight to tenfold [increased] lifetime risk of developing bipolar disorder" (p. 2)
- The diagnosable onset of bipolar disorder is consistent with the classical perspective: "the index manic or hypomanic episode typically manifests in mid-late adolescence and early adulthood." (p. 7)
- However, "episodes are often preceded by years of clinically significant psychopathology at both the syndrome and symptom levels." (p. 7)
- Such psychopathology includes "emotional sensitivity and sleep and anxiety disorders in childhood, followed by depressive disorders" in early-mid adolescence, and further,

"more proximal prodromal hypomanic symptoms manifest prior to the full-threshold hypo/manic episode" (pp. 7-8)

- Clearly identified "psychological risk processes", or personality/behavioural traits, include "rumination, self-appraisal processes, impulsivity, and reward sensitivity" (p. 8)
- Such non-specific syndromes and risk traits only have "predictive meaning in children at confirmed familial risk" (p. 8)
- "In contrast to psychotic illnesses, cognitive deficits in bipolar disorder emerge after full-blown illness onset" (p. 8)
- However, antecedent neurodevelopmental deficits occur in "spectrum bipolar" (p. 8), in other words schizoaffective/psychotic spectrum cases.

These findings map out precursors of non-specific syndromes and temperamental antecedents to bipolar disorder and schizoaffective disorder. They point to further research to explore the early identification and intervention possibilities.

Duffy and colleagues proposed that differentiating early signs of classical episodic bipolar disorder from "spectrum bipolar" is becoming possible. Notably, what they are defining as "spectrum bipolar" is on a spectrum with psychotic disorders such as Schizoaffective disorder and schizophrenia. This is quite different to the "soft bipolarity" neurotic domain of dysfunction of what is commonly called bipolar spectrum disorders in adult psychiatry and includes the hypothesised PBD phenotypes in child psychiatry. Duffy et al. made that point strongly in this review:

> [Despite] … repeated prospective direct assessment of children at confirmed familial risk, these studies have almost uniformly found no support for the proposed pre-pubertal or very early onset bipolar disorder subtype (Duffy et al. 2014; Egeland et al. 2012; Mesman et al. 2013). For example, the mean age of onset of the first diagnosable activated episode across studies at last report ranged from 13 to 20 years (Duffy et al. 2014; Mesman et al. 2013; Nurnberger et al. 2011). (p. 6)

The Pittsburgh PBD research group's findings did not correlate with the findings of the Canadian, Dutch, US Amish and US Indiana University multisite studies:

> The BIOS study stands apart somewhat from these other published studies reporting that, in those offspring who developed BD, 50% had mania prior to age 12 (compared to 0% in other studies) and 50% debuted with a depressive episode (compared to over 80% in other studies) (Axelson et al. 2015). (p. 6)

This highlights that the sole offspring study that utilised the PBD hypothesis was the outlier amongst these six offspring studies in being the only study to regularly find pre-adolescent cases of bipolar disorder. What the Pittsburgh BIOS study had reported in 2015 about age of onset was the following:

> [T]he mean age of onset of mania/hypomania was 13.4 ± 3.8 years and the first onset of bipolar spectrum disorder was 12.1 ± 4.0 years. The mean age of onset of the first major depressive episode was 13.7 ± 4.0 years and the first onset of any depressive episode (major depressive episode or minor depression) was 12.5 ± 4.6 years. Of the 15 high-risk offspring who had a manic episode, 5 (33%) had the first episode prior to age 10 and 8 (53%) had it prior to age 12, with the earliest at age 8.1. (Axelson et al., 2015). (p. 7)

Axelson et al. reported that 36% of those who developed a full manic/hypomanic episode had earlier "subthreshold (hypo)manic episode" (p. 7) but did not give the specific ages of onset. While these ages are lower than the other offspring studies, they do appear to be not as young as the preschool age of onset for many of the earlier MGH-Harvard and WUSL PBD cohorts. One hypothesis here would be that the Pittsburgh group have gathered more cases of classic bipolar disorder into their cohorts than the MGH-Harvard or WUSL groups did.

However, Duffy et al. (2017b) noted the Swiss study did find a half dozen peripubertal cases of hypomania/mania prior to age 12, raising the importance of recognising trauma:

> [T]he mean age of onset of the first diagnosable activated episode was age 16 (SD 5.1 years), of which 61% debuted with a depressive episode. Six cases (19.4%) of mania/ hypomania were found prior to age 12, but 5 out of these 6 children had experienced early trauma just before the reported onset of mania/hypomania. The mean age of onset of the first activated manic/hypomanic episode in the remaining offspring was 17.5 (SD 4.3) years. With longer follow-up, the mean age of onset of first activated episode will likely increase further… (p. 6)

In email communication with Caroline Van De Leur from the Swiss group, it was clarified that two of the cases had informant discrepancies (the child and later as adolescent denied the episodes). The other four cases occurred in response to severe trauma. None of the six cases had yet suffered recurrence over the years since (C Van De Leur, 2018, personal communication, 17 February). This data set is evocative, as it suggests that trauma and maltreatment factors may either precipitate the onset of genuine bipolar disorder, or cause mood and behavioural dysregulation that may be misdiagnosed as a hypomanic/manic/mixed episode, or both. The Czech study (Goetz et al., 2015) supports the hypothesis that trauma and maltreatment factors can precipitate an earlier onset of true bipolar disorder.

4.8.8 **Debate over community epidemiological prevalence of PBD**

4.8.8.1 **Van Meter, Moreira & Youngstrom (2011) meta-analysis of epidemiological studies**

However, an article published in the *Journal of Clinical Psychiatry* was to strongly reassert the view that PBD is a common and widespread global condition. Researchers from the University of North Carolina performed a meta-analysis of a dozen community epidemiological studies of psychiatric disorders primarily in the adolescent to young adult age range, with three studies including pre-pubertal children (Van Meter, Moreira & Youngstrom 2011). Six were US studies and six were from other nations. This meta-analysis has been widely cited (307 *Google Scholar* citations as of 5 August 2019) mostly to support the idea that PBD is common, affecting 1.8% of the world's children and youth.

A narrative re-examination of the studies in this paper comprises Chapter 6 of this thesis. Substantial differences between the studies meant that the necessary homogeneity requirements for meta-analysis were not satisfied, hence invalidating the results. A re-interpretation based on corrected methodology in the 12 studies gave individually vastly lower prevalence rates of bipolar disorder in most studies, particularly before late adolescence (Parry, Allison & Bastiampillai 2018a; Appendix A31).

4.8.8.2 **Debate on PBD epidemiology and validity in *CAMH***

4.8.8.2.1 **Carlson Commentary on Parry et al. (2018) *CAMH***

Gabrielle Carlson in early 2019 is the president-elect of AACAP. As has been noted (Chapter 3.1), she was one of the researchers to pose the PBD hypothesis as a research question in the 1980s, but later became a staunch critic of the PBD epidemic. She published a commentary article in *Child and Adolescent Mental Health* titled: "Bipolar disorder in youth – what is it and where is it? – a commentary on Parry et al. (2018)" coinciding with the hard copy publication of our re-analysis of Van Meter et al.'s (2011) meta-analysis (Parry, Allison & Bastiampillai 2018a; Appendix A31; Chapter 6).

She noted that the "widely cited meta-analysis" of Van Meter et al. reports rates of PBD at "about 1.8% in the United States and the rest of the world" and the "premise of the meta-analysis is to debunk the notion that bipolar disorder rates are higher in the United States than elsewhere" (p. 23). She then described our re-analysis of the original studies:

> Parry, et al. debunk the debunking and present data that the conclusions are false because the studies included were misrepresented and that the meta-analysis combined studies that differed sufficiently methodologically that combining was inappropriate. Parry, et al. conclude that you cannot really draw a conclusion, but if you do, rates of mania/bipolar I disorder are lower in both places than referenced by Van Meter, et al. Lifetime rates in most adolescents within the United States are between 0% and 1% and outside the United States between 0% and 0.1%. Bipolar spectrum definitions were inconsistent. (p. 23)

Carlson critiques the combining of almost completely discrepant parent and teen informant results as "specious" and noted the original epidemiological "studies' authors themselves concluded that the rates they obtained for mania were not accurate" (p. 23). In an echo of her 1998 critique of reliance on structured clinical interviews for diagnosing PBD (Carlson 1998), she noted:

> [P]urportedly 'gold standard' semi-structured interviews such as the K-SADS-E or WASH U KADS don't do a very good job of defining episodes of mania or differentiating bipolar disorder from hyperkinetic conduct disorder for example. (pp. 23-24).

She referred to the ubiquitous problem of reification in psychiatric nosology, and that despite the noble aims of DSM-III to provide more accuracy in diagnoses, this problem persists:

> "[M]eeting the criteria" for something on a structured interview does not mean having the disorder, a point made by Kendler (2016). He stated "since DSM III, our field has moved toward a reification of the DSM that implicitly assumes that psychiatric disorders are just the DSM criteria. That is, we have taken the index of something for the thing itself." The most insidious part of that insight is that several generations of clinicians have had the template of bipolar disorder readjusted to be what the criteria say, depending on the viewpoint that has held sway in the department where they trained. (p. 24)

Carlson concluded:

> As a hypothesis, the possibility that many explosive children had bipolar disorder was not unreasonable and testable. The error comes only from concluding it is a certainty, interpreting everything through that lens and thinking you have solved a problem which has not been solved. Dr. Parry and company will perhaps feel relieved that some of the hypothesizers are keeping an open mind. (p. 25)

It indeed was a relief for me and my colleagues to know that the president-elect of AACAP, who had one of the most experienced longitudinal perspectives of the PBD phenomenon, was astutely appraising the issues.

4.8.8.2.2 Nine-article debate on PBD in *CAMH* issue 1, 2019

Our re-analysis of the 12 epidemiological studies and Carlson's editorial commentary, led to a response article by Van Meter and colleagues (Van Meter, Moreira & Youngstrom 2019a). We were invited to respond to Van Meter et al.'s response (Parry, Allison & Bastiampillai 2019a; Appendix A34) and in the accompanying "Debate Editorial" titled "Very early onset bipolar disorder – international differences in prevalence, practice or language?", Carlson and Dubicka (2019) stated:

> CAMH has instituted a new feature called 'the Debate'. … The first topic is on the subject of bipolar disorder in children and whether or not there are actual international differences in prevalence, or international differences in diagnostic practice. The topic arose from an article written by Parry, Allison, and Bastiampillai

> (2018), which took issue with an older meta-analysis by Van Meter, Moreira, and Youngstrom (2011). (p. 88)

They also requested articles from: Birmaher (Pittsburgh) "known for both longitudinal and high-risk studies on children and adolescents with bipolar disorder" and his colleague (and chair of the ISBD Task Force on PBD) Goldstein (Toronto); from Hazell P (Sydney) "who has written about children with possible mania for 20 years"; "two high-risk [offspring] researchers" Duffy (Canada) and Hillegers (Netherlands); Pan and colleagues (Brazil) who have researched the community prevalence of bipolar disorder in children with "methodology similar to Stringaris [et al.] (2010)"; and Stringaris for his "methodological and epidemiologic expertise, as well as having a foot on both sides of the Atlantic [London and NIMH]" (p.88). This was the most comprehensive debate in the literature since the 1998 *JAACAP* debate between Biederman (1998a, 1998b) and Klein RG, Pine and Klein (1998a, 1998b) (Chapter 4.8.2.2).

Van Meter, Moreira and Youngstrom (2019a) titled their response "Looking forward: choose data over opinions to best serve youth with bipolar spectrum disorders – commentary on Parry et al. (2018)". They defended the methodology of their 2011 meta-analysis as incorporating measures accounting for heterogeneity of methods in the original epidemiological studies. They criticised our re-analysis article for:

> [R]epeatedly report[ing] the rate for bipolar I that they believe is the 'true' rate and compare it unfavorably to the rate included in the meta-analysis, without noting the fact that the meta-analysis included both the rate they support and the broader (usually higher) rate for the full bipolar spectrum. (p. 89)

This is a reasonable criticism in that we made the point that the hypothesised PBD phenotypes that fit into the Bipolar-NOS framework are too non-specific in externalising and internalising symptomatology. We felt it was important to therefore differentiate between where the epidemiological surveys recorded Bipolar-I disorder and the rest of the 'bipolar spectrum disorders' (Parry, Allison & Bastiampillai 2018a; Table 1; Appendix A31; Chapter 6.4.1).

Van Meter, Moreira and Youngstrom (2019a) argued that "pediatric bipolar disorder is real, its effects can be devastating, and it affects children and families worldwide" and that too many clinicians were not up to date with the "literally thousands of papers" published on PBD

(p. 90). Missing very-early-onset cases is therefore a serious problem. We agreed in our response that "there is often a long delay in diagnosing BD, and clinical vigilance is vital" (Parry, Allison & Bastiampillai 2019a, p. 92). We noted "however, premature and incorrect diagnosis of BD can harm children" and listed iatrogenic consequences of inappropriate pharmacotherapy, of labelling, missing alternative diagnoses and psychosocial contextual factors such as maltreatment (p. 92).

Goldstein, Post and Birmaher (2019) in their article titled "Fomenting controversy regarding pediatric bipolar disorder", supported Van Meter, Moreira and Youngstrom (2019a) for "a measured, thoughtful and restrained response" to our re-analysis of their meta-analysis. They critiqued our 2018 re-analysis as "outdated invective" which:

> [M]eanders from epidemiologic studies, to administrative claims and hospitalization datasets, to commentaries regarding some of the American clinical studies from a quarter century ago that brought the concept of childhood bipolar disorder to the fore. (p. 95)

They "highlight[ed] three additional areas of concern", namely that we had: "espous[ed] doubts regarding the existence of bipolar disorder in children"; "[made] false assertions regarding expected age of onset and prevalence of bipolar disorder"; and "minimiz[ed] the impairment and severity of the bipolar spectrum"(p. 95). With regard to age of onset, Goldstein et al. made reference to Kraepelin's findings:

> Parry et al.'s abstract concludes 'the reanalysis suggests that bipolar disorder is rare before the expected age of onset in later adolescence'. Kraepelin himself stated that the peak onset of bipolar disorder begins at age 15, and acknowledged occurrence in childhood. Perhaps, Parry et al. would characterize Kraepelin as a 'mindless' psychiatrist – we do not. (p. 95)

Van Meter et al. (2019) had also cited Kraepelin and in our response we had indicated that Kraepelin's findings were that pre-pubertal cases existed but were extremely rare:

> Van Meter et al. (this issue) referenced the seminal study of Kraepelin as including 'descriptions of prepubertal cases'. However, Kraepelin only reported another German psychiatrist describing a single case (Kraepelin, 1921, p. 167). Kraepelin

> provided age of onset of manic-depressive insanity (p. 168), based presumably on patient recall histories (Parry et al., 2019a, pp. 92-93).

We listed Kraepelin's statistics (Chapter 2.1) of minimal rates prior to age 15. Additionally we reiterated that the 'administrative prevalence' rates in several countries (as presented in Chapter 4.8.6.14 above) were in fact what was diagnosed amongst inpatient cases by child psychiatrists and were "100- to 900- fold less in preadolescents and 30- to 300-fold less in young adolescents" in a range of countries compared to the US (p. 92).

At this point the *CAMH* debate reflected the 'liberal' perspective, to use the parlance of Carlson and Klein (2014) of PBD researchers versus the 'conservative' perspective that we were presenting with divergence somewhat along geographic lines. Hazell P (2019), also from Australia, but having 20 years ago conducted a follow-up study of 'broad' phenotype PBD adolescents who did not progress to bipolar disorder in young adulthood (Hazell, P et al. 2003), weighed in. He suggested that after two decades both the ultradian cycling variant as well the chronically irritable variant of PBD had not been proven to be bipolar disorder.

Hazell P (2019) suggested that: "the use of the term bipolar in this context (even in 'bipolar spectrum' or 'broadband bipolar') carries with it erroneous assumptions about aetiology, associations, treatment and prognosis". Therefore, he proposed "an eponymous naming convention" for these PBD phenotypes of "Geller-Wozniak syndrome (GWS)" be used in order to differentiate them from: "paediatric bipolar disorder (BD) that may apply to a young person in their mid-adolescence presenting with classic features of what was once called manic depressive illness" (p. 97). Further, he suggested that 'GWS' cases be defined by consensus and followed up both longitudinally and also cross-nationally to observe the outcome as to whether they do or do not represent early harbingers of later bipolar disorder.

Duffy (2019) described how with the advent of DSM-III and later editions, symptoms of affective instability and irritability were divested from the diagnostic category of ADHD or hyperkinesis, and this later led to the creation of the PBD and SMD/DMDD diagnoses. She stated: "*the critical question is not if these symptoms exist in prepubertal children, but do these symptoms have anything at all to do with bipolar disorder?"* (p. 99, italics in original). She reiterated the finding from "multiple prospective longitudinal high-risk studies of the children of bipolar parents" which found prepubertal cases of bipolar disorder to be

"exceedingly rare or completely absent". She summarised the findings of "longitudinal follow-up studies of clinically referred children" that neurodevelopmental disorders increase risk for adulthood psychosis and ADHD increases risk for adulthood ADHD, depression and substance-use disorders, but neither increase the risk for bipolar disorder (p. 100). She concluded:

> The elephant in the room is that there is no evidence from high-risk or clinical longitudinal studies or from imaging or genetic studies to support that this pediatric bipolar phenotype has anything to do with adult bipolar disorder. (p. 100)

Hillegers (2019) is a researcher from the Netherlands on the Dutch offspring study. She reiterated the discrepancy between the US tendency to diagnose PBD whereas "in Europe, we also see such emotional dysregulated children" but in contrast they are "diagnosed within the disruptive behaviour ADHD/ODD/CD spectrum" (p. 101). Hillegers referred to Mesman et al. (2016) of which she was a co-author that compared the Pittsburgh and Dutch offspring studies, noting the parents in the Pittsburgh study were more likely than the Dutch parents to have Bipolar-II or Bipolar-NOS than Bipolar-I disorder as well as high rates of co-morbid psychopathology, substance use and unemployment and the Pittsburgh co-parents without a bipolar disorder diagnosis had high rates of other psychopathology compared to Dutch parents. Hillegers concluded:

> These differences illustrate the importance of the psychopathology load of both the parents, the level of family functioning, and stress and effect of the recruitment strategy in under- standing rates of offspring psychopathology and com- paring cohorts. (p. 101)

Hillegers also described a recently published Danish longitudinal high-risk offspring study of 522 prepubertal children (Ellersgaard et al. 2018). There were 202 children of parents with 'schizophrenia-spectrum disorders', 120 children of parents with bipolar disorder and 200 children of control parents. Although in its early stages none of these children, with an age range of 6.9 – 8.4-years-old, had been diagnosed with bipolar disorder, despite symptoms of stress, anxiety and adjustment disorders. Diagnoses were based on the K-SADS-PL, Child Behaviour Checklist (CBCL) and CGAS (Child Global Assessment Scale; Shaffer et al., 1983) as well as teacher reports and other scales. In concert with the findings of the Canadian high-risk offspring study, the children of schizophrenia-spectrum disorders had a higher incidence

of ADHD (20.6%) and 2 were diagnosed with 'psychotic disorder NOS', whereas the rate of ADHD in the bipolar disorder offspring (9.3%) and control parent offspring (7.1%) were similar (Ellersgaard et al. 2018, p. 215).

Pan, Salum and Bressan (2019) are researchers in the Brazilian High-Risk Cohort Study for Psychiatric Disorders (HRC) (Pan et al. 2014). This study used similar methodology and the DAWBA (Development and Well-Being Assessment; Meltzer et al., 2000) instrument as Stringaris, Santosh, et al. (2010) in England. Pan et al. compares the results of the Brazilian cohort of two thousand five hundred three 6 – 12-year-olds by parent-report only (0.2% prevalence of bipolar disorder, 1.6% of Bipolar-NOS) with results from those in the English cohort of five thousand two hundred forty seven 8 – 19-year-olds (0.1% Bipolar-I/Bipolar-II, 1.1% by parent-report or 1.5% by youth-report Bipolar-NOS). Pan et al. describe the attenuated phenomenology of the Bipolar-NOS cases in both studies raises doubts as to whether they will ultimately evolve into bipolar disorder.

Stringaris (2019) noted the similarities of the English and Brazilian studies, particularly with regard to the Bipolar-NOS cases:

> [A]s did Pan et al., we had well over 1% of young people with BP-NOS by parent- or self- report. In other words, the vast majority of people in epidemiological surveys are and should be viewed as being of yet uncertain relationship to classical, noncontroversial bipolar disorder. (p. 106)

Stringaris lamented that in the UK the idea of a child having bipolar disorder was usually dismissed. However, citing Lohr et al. (2015) regarding the high rates in Kentucky of antipsychotic prescribing in "the younger than 7-year-olds" and Ray et al. (2019) regarding the "4.29 hazard ratio for death" due to these agents, he criticized the PBD overdiagnosis problem in the US for leading to likely "devastating consequences" (p. 106).

4.8.8.3 **Van Meter et al. (2019b): Updated meta-analysis *J Clin Psychiatry***

Van Meter and colleagues published an updated version of their 2011 meta-analysis in the same *Journal of Clinical Psychiatry* online on 2 April 2019 (Van Meter, Moreira & Youngstrom 2019b). They included the six extra epidemiological studies that the ISBD PBD Task Force did, added two more (Vizard, Pearce, et al. 2018; Karacetin et al. 2018) and removed the New

Zealand study (Kim-Cohen et al. 2003) for a total of 19 studies. On the basis of "more advanced statistical methods" that took into account that some studies did not report on the full bipolar spectrum, they found the prevalence rate for bipolar spectrum disorders increased to 3.9% (p. e6).

However, in this updated version they reported prevalence rates for Bipolar-I disorder of 0.6% and combined Bipolar-I/Bipolar-II of 0.7%. Further, they noted: "Fourteen studies reported on the rate of bipolar I disorder. Of these 4 reported zero cases, and 3 reported just 1 or 2 cases" (p. e6). The fact that "the rate of bipolar I disorder (0.6%) is lower than the rate reported in the 2011 meta-analysis (1.2%)" was because the "6 [new studies] that reported bipolar I separately ... contributed over 27,000 participants, but only 53 cases of bipolar I" (p. e7). In particular, the two latest studies of Vizard, Pearce et al. (2018) in the UK and Karacetin et al. (2018) in Turkey respectively reported only a British Bipolar-I rate of 0.1% among nine thousand one hundred seventeen 5 – 19-year-olds and no Turkish cases of Bipolar-I, Bipolar-II or Bipolar-NOS in five thousand eight hundred forty two 8 – 10-year-olds.

In their discussion Van Meter et al. (2019b) note the lack of bipolar spectrum disorder cases among pre-adolescent children, the problems of parent and youth informant discrepancies, and the differing perspectives that clinicians and researchers bring, even when using the same structured clinical interviews. They comment that the two newest studies (Vizard, Pearce et al. 2018; Karecetin et al., 2018) "have very low rates" (p. e6). These studies had large numbers of pre-adolescent children. Van Meter et al., based on "funnel plots and Egger test", interpreted these and other large studies to have "bias" towards "lower-than-expected prevalence rates" (p. e6). They speculated that "very large studies may rely on more structured diagnostic methods and lay raters that are more likely to miss case of PBD" (p. e7).

Van Meter, Moreira and Youngstrom (2019b) also noted the rates reported from the epidemiological studies were statistically heterogenous for both bipolar spectrum disorders (Q = 759.82, df = 32, P <.0005) and for Bipolar-I (Q = 154.27, df = 13, P <.0001). Despite this marked heterogeneity, the first two of their three bulleted 'clinical points' spoke of constancy and uniformity in PBD prevalence rates across time and geography:

- The prevalence of pediatric bipolar disorder in the community has been relatively constant over time.

- The prevalence of pediatric bipolar disorder is not higher in the United States than it is in other countries. (p. e2)

With respect to their second 'clinical point', they cited our 2008 article titled "Pre-pubertal paediatric bipolar disorder: a controversy from America" (Parry & Allison 2008; Appendix A2) as "one of the primary drivers for doing the 2011 meta-analysis was the international perception that PBD was a creation from the United States" (p. e7). Yet, in this updated article they also cited Post et al. (2017) that "there is some evidence from other studies that very early onset is more likely among youth in the United States" but "because the majority of youth represented in this study were adolescents, any differences in prevalence among prepubescent youth were not captured" (p. e7).

Their third 'clinical point' acknowledged the problems with heterogeneity:

- Knowledge about the community prevalence of pediatric bipolar disorder is limited by the lack of studies from non-Western countries, the inconsistency in measurement across studies, and the small number of studies that include prepubescent youth. (p. e2)

In the same manner that the first meta-analysis by Van Meter, Moreira and Youngstrom (2011) was re-analysed via a narrative analysis of the original dozen epidemiological surveys (Parry, Allison & Bastiampillai 2018a; Appendix A31; Chapter 6), a narrative analysis of these eight new epidemiological studies from Van Meter et al. (2019b) is presented in Chapter 6.8 in Part II of this thesis. Next, however, is a summary of recent debates on the validity of PBD.

4.8.9 **Recent academic debate on validity of PBD**

4.8.9.1 **Amerio et al. (2016) and Parry et al. (2016) in *ANZJP***

The Australasian psychiatric literature had little published on the topic of PBD following the initial articles in 2007 and 2008 (Chapters 4.8.6.3; 4.8.6.5) However, in 2016, a review of treatment of comorbid PBD and OCD by US and Italian researchers was published in the *ANZJP* (Amerio et al., 2016). We critiqued the review in a letter (Allison et al., 2017; Appendix A29), a section is transcribed here:

> Amerio et al. reviewed the treatment of children and adolescents (aged 4–17 years) diagnosed with both paediatric bipolar disorder (PBD) and obsessive-

> compulsive disorder (OCD). They report Osler's view, '*medicine should be treatment of diseases, not of symptoms*' (p. 594), and, on this basis, recommend treating PBD as the underlying disease, using adult mood stabilisers for children and adolescents.
>
> Osler's view is highly relevant to PBD: Is PBD really a 'disease' or just a loose collection of common 'symptoms' such as irritability and mood lability that arise from many causes in childhood?... (p. 98)

We suggested that it would:

> be difficult to predict a low prevalence condition like adult BD from high prevalence childhood symptoms such as irritability and mood lability measured decades earlier (Malhi, 2016). (p. 98)

By definition, it is challenging to predict relatively rare outcomes from variable collections of frequently occurring antecedents.

4.8.9.2 **Malhi in *The Lancet* and *Bipolar Disorders* 2016-2017**

We had cited Professor Gin Malhi (Sydney University), chief-editor of the *ANZJP.* Malhi has maintained a research interest in bipolar disorder and was co-author to articles that were cautiously open to the PBD hypothesis in the mid-2000s (Cahill, Green et al., 2007). Therefore, he was well familiar with the PBD hypothesis, and consequently it is particularly noteworthy that in 2016 he cautioned against the diagnosis of PBD in an opinion piece in *The Lancet* (Malhi, 2016). Malhi stated that non-specific mild mood presentations make diagnosis "more complicated in adolescence, when the brain is still developing" (p. 1492). Regarding children he stated:

> The diagnosis of bipolar disorder has been at the centre of recent controversy, particularly in children, in whom the illness is referred to variably as paediatric bipolar disorder, juvenile bipolar disorder, or early-onset bipolar disorder… Within a decade, this variant became the most common diagnosis in children younger than 12 years who were admitted to hospital for psychiatric diagnoses in the USA.[8] A principal reason for this startling escalation in diagnosis was a paradigm shift by key US researchers. (p. 1492)

Malhi criticised the chronic irritability basis for PBD. He also included the WUSL group and ultradian-cycling, by referencing Geller et al. (2008)'s article in *Archives of General Psychiatry* (reference 12 in this quote):

> Some US experts still suggest that paediatric bipolar disorder is best defined by chronic, non-episodic, mixed irritable states that cycle rapidly.[12] (p. 1493).

In addition to being chief-editor of the *ANZJP,* Malhi is also an editor-in-chief for *Bipolar Disorders*. In a literature review in *Bipolar Disorders,* titled "Is 'early intervention' in bipolar disorder what it claims to be?", Malhi and co-authors cautioned that despite the "understandable" "enthusiasm for early identification and intervention strategies" (Malhi et al., 2017, p. 629) for bipolar disorder, the "evidence" was "limited" (p. 631). He was particularly critical of "prescribing pharmaceuticals to younger populations without first having robust empirical support for their efficacy" (p. 632), saying "the lack of empirical evidence to support the efficacy of these medications … among children and adolescent populations is concerning" (p. 632).

Figure 4.35, from Malhi et al. (2017) graphically illustrates that while underlying neuropathological and genetically driven processes may be progressing, the visible clinical symptomatology of bipolar disorder meant certainty of diagnosis did not manifest until late adolescence or adulthood.

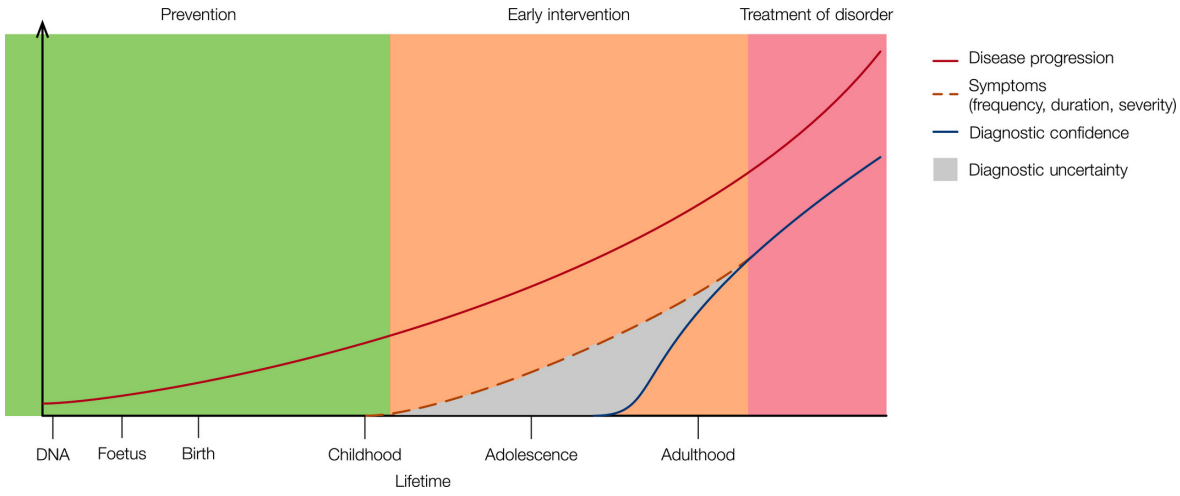

Figure 4.35: Defining early intervention in bipolar disorder (BD) (Malhi et al., 2017, p. 630). Reproduced with permission.

4.8.9.3 **ISBD Task Force on PBD report in *Bipolar Disorders*, 2017**

A few months later, Wozniak was one of 18 authors comprising a special 'task force' representing the leading PBD research centres, that published a major review of the PBD literature to date. The review was titled: "International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder" (Goldstein et al. 2017). Given the prominence of this ISBD Task Force report, at the quarter century mark of the PBD hypothesis, an in-depth critique follows. Several lacunae in the review, and the research it summarised, appeared evident.

4.8.9.3.1 **Minimal discussion of offspring studies**

At 19 pages and with 261 references, Goldstein et al. (2017) was a substantial document. Given the length, it was surprising there was no mention of the international clinical diagnosis studies. It was also surprising that the ISBD Task Force stated that "systematically addressing the topic of offspring of parents with BD was beyond the scope of this article" (p. 532). The only reporting of the longitudinal offspring studies was: firstly, of the Dutch study simply being cited (Hillegers et al. 2005) to indicate that there were international data on "high-risk studies" (p. 526); and secondly, the reporting of a study comparing the Pittsburgh (BIOS) offspring cohort with the Dutch offspring cohort (Mesman et al. 2016). Goldstein et al. (2017) noted that:

> After controlling for age, rates of DSM-IV BD-I (2.2% in the US sample and 1.5% in the Dutch sample) and BD-II (2% and 1%, respectively) were similar. In contrast, other disorders were significantly more common in the US sample, including depressive disorders (13% vs 4% in the Dutch sample), anxiety disorders (31% vs 9%, respectively), ADHD (22% vs 8%, respectively), and disruptive behavior disorder (19% vs 6%, respectively). CBCL Externalizing scores were higher in the US sample… In the US, fewer parents had BD-I, affected parents were younger at their own illness onset, parental substance abuse rates were higher, and rates of parental employment and youth living with both biological parents were lower. These stressors may have contributed to the greater rates of problems in the US sample. (p. 526)

In other words, the Pittsburgh offspring cohort appear to have families with more psychosocial stress and substance abuse and have higher rates of behavioural dysregulation than the Dutch cohort. By "controlling for age" what the ISBD Task Force did not mention was that age of onset in the Dutch cohort was significantly older than for the Pittsburgh cohort, as had been discussed by Duffy et al. (2017). Mesman et al. (2016) give age of onset for the US sample as 50% before age 19 years, compared to 26% before age 19 for the Dutch sample (Mesman et al. 2016; Table 1). The breakdown of age of onset within the paediatric age range for the Dutch offspring study is given in Mesman et al. (2013). Of 17 young Dutch offspring who have so far developed a bipolar spectrum disorder, four were Bipolar-I, 11 Bipolar-II, one Cyclothymia and one Schizoaffective disorder. The age of onset of first manic/hypomanic episodes were late teens to twenties, the youngest being the case of schizoaffective disorder with an onset at age 13. The mean age of hypomania/mania onset for the cohort so far is 19-years, range 13 – 31-years (p. 545). This mean age is likely to rise if other Dutch offspring manifest hypomanic/manic episodes in future. This is a starkly different group to the Pittsburgh BIOS cohort with a reported mean age of onset of 13.4(±3.8)-years and the first onset of bipolar spectrum disorder was 12.1(±4.0)-years (Axelson 2015, p. 7).

In a debate article we submitted to *Bipolar Disorders*, we noted that it was unfortunate that Goldstein et al. did "not systematically review the bipolar offspring studies" as they showed that "mania is rare before puberty", although high-risk children may experience "sleep and anxiety disorders" (Parry, Allison, Bastiampillai 2018b; p. 1; Appendix A33).

4.8.9.3.2 "Tremendous growth in the scientific literature" regarding PBD

The Task Force reported "tremendous growth" (p. 524) of the PBD literature over the "past two decades" that "now contains numerous gold-standard clinical trials of pharmacological agents for mania, an increasing evidence base for adjunctive psychosocial treatments" (implying pharmacotherapy is the first-line aspect of treatment), "large-scale prospective clinical cohort studies" and "numerous neurocognitive and neuroimaging" and "biomarker studies" (p. 525). The almost exponential growth of PBD publications was presented in a graph (Figure 4.36)

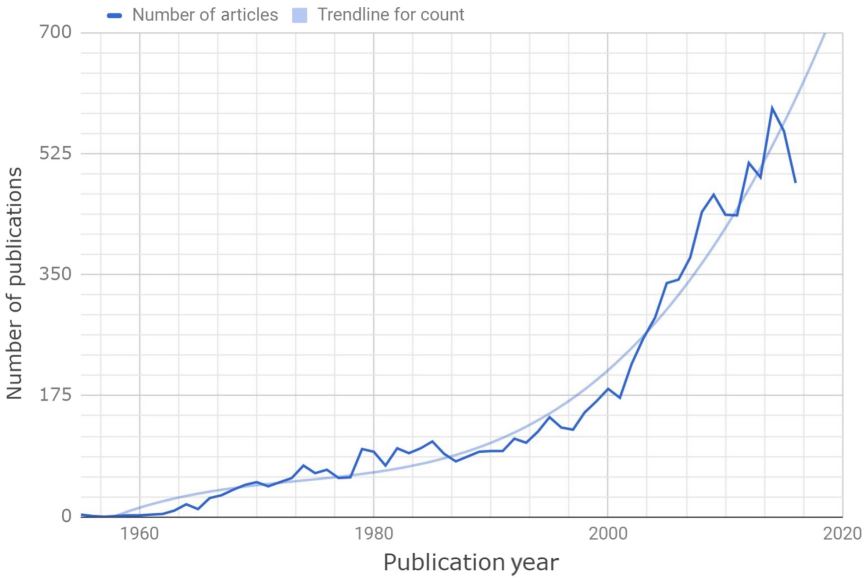

Figure 4.36: Articles about pediatric bipolar disorder indexed in PubMed each year (Goldstein et al. 2017, p. 521). Reproduced with permission.

The search terms used for this graph were wide and would have picked up articles that referred to bipolar disorder in the paediatric age range that were not in line with the PBD hypothesis. It produces the same pattern I found with a Scopus search (2 March 2018) using the same terms: ("bipolar disorder" OR mania or manic) AND (child OR adole* OR pediatric OR juvenile) for articles to end 2017. Early articles from the years 1884, 1913, 1915 were excluded, the articles next began in 1931. (Figure 4.37).

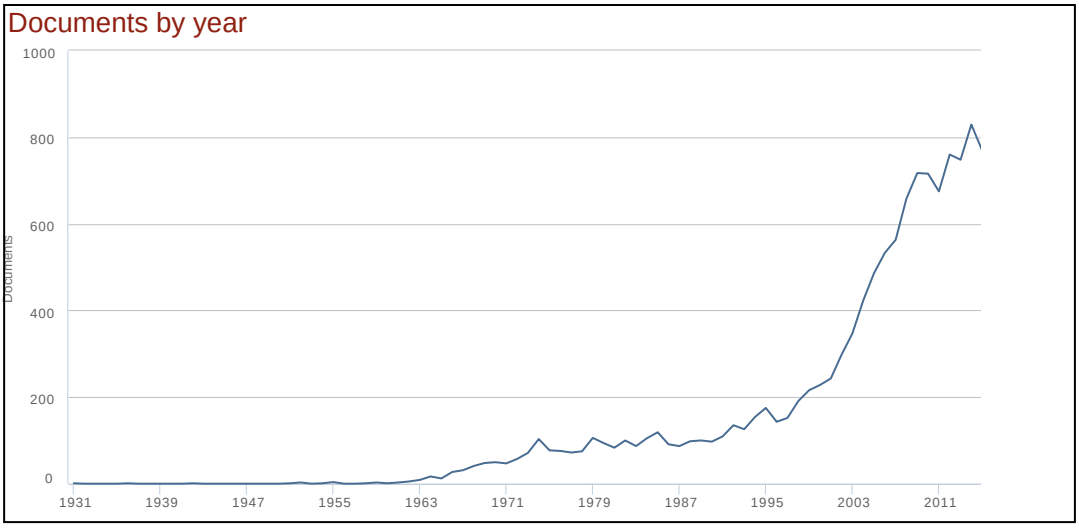

Figure 4.37: Number of published articles on bipolar disorder in paediatric age range based on Scopus search

Whereas the graph for more specific PBD literature ("paediatric bipolar" OR "pediatric bipolar" OR "juvenile bipolar" OR "childhood bipolar" OR "paediatric mania" OR "pediatric mania" OR "childhood mania" OR "juvenile mania") shows a peak and fairly steep decline beginning in 2009 (Figure 4.38), reproduced here for easy comparison. The first articles for this search dated from 1977.

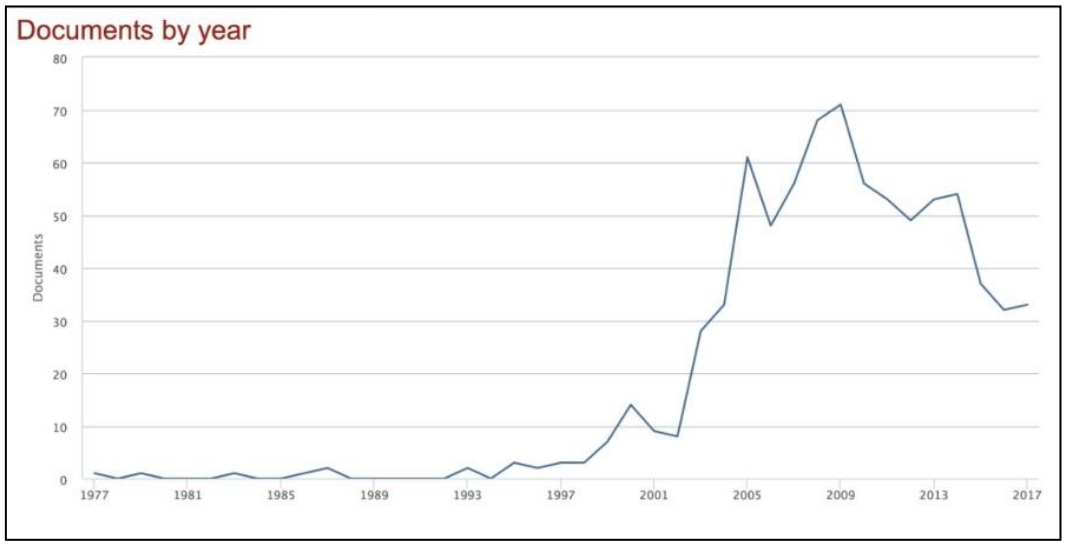

Figure 4.38: Number of published articles on bipolar disorder in paediatric age range based on Scopus search with high specificity

The point being made here is that the PBD hypothesis literature is more circumscribed than the literature that included the classical perspective. Furthermore, there has been a marked decline since 2009, which is not reflected in Goldstein et al.'s task force report on PBD.

4.8.9.3.3 Epidemiology still modelled on Van Meter et al. (2017)

The ISBD Task Force stated that it wanted to dispel the "myth" that PBD "doesn't happen in children" and staked their argument on "epidemiologic samples in ages 5 years and higher" (p. 529). The report cited Van Meter et al. (2011), and that the 12 epidemiological studies had been updated with "six new studies" to make a total of:

> [18] studies (seven from the USA) with 31,443 youth aged 7-21 years, 576 of whom met criteria for bipolar spectrum disorders.[2-17] The updated weighted average prevalence rate of bipolar spectrum disorders is 2.06% (95% confidence interval [CI] 1.44%-2.95%). (pp. 525-526)

On this basis, it was claimed that "PBD prevalence rates appear relatively stable across studies" and "community rates are not higher in the USA… PBD is more common than autism or schizophrenia and much less common than depression or ADHD". They noted "heterogeneity" in the studies and that "more data are available with post-pubertal samples, and they find higher rates than before puberty" (p. 526).

There were several factors contributing to the high prevalence estimate cited by Van Meter et al. (2011)'s meta-analysis. We noted that:

> The prevalence estimate was high because several of the epidemiological studies, firstly, used broad definitions of BD; secondly, combined parent and child reports, even if they were discordant; thirdly, used only youth informants; and/or finally, did not apply impairment criteria. (Parry et al. 2018b, p. 1)

More recently, we conducted a similar narrative analysis of the six extra epidemiological studies that the ISBD Task Force on PBD had added to the original dozen epidemiological studies (Parry, Allison, Bastiampillai 2019c; Appendix A36). Our findings for these six studies are provided in Chapter 6.8. Suffice to say here, we found lower rates than the Task Force.

4.8.9.3.4 "Established … international consensus" … or not?

The Task Force aimed to also dispel the "myth" that there was "no evidence outside of US" for PBD (p. 529). Citing Diler's book (Chapter 4.8.6.4) they reported:

> [T]here now are PBD data from multiple countries including Australia/NZ, Brazil, China, France, India, Italy, South Korea, Spain, the Netherlands, Turkey, and the UK (Diler, 2007) (p. 527).

However, as the authors of each chapter in Diler's book on global perspective on PBD indicated, the PBD hypothesis was generally not accepted or at least controversial in their respective countries. As will be further elucidated in Chapter 7 and in Parry, Allison and Bastiampillai (2019b; Appendix A35), the acceptance of the PBD hypothesis outside the US has been quite limited.

Although this was an ISBD task force, 14 of the 18 authors were from US institutions, and of the four non-US authors: Canadian Goldstein is also affiliated with the University of Pittsburgh

group; British author Perez-Algorta had been affiliated with Ohio State University and is an adjunct assistant professor at the University of North Carolina where ISBD Task Force co-author Youngstrom is lead researcher; Professor HW Kim is from the University of Ulsan in Seoul, South Korea and has co-authored PBD research with Korean children with Youngstrom (who is now a visiting professor to Korea University, Seoul) and with Findling from Ohio (Lee et al. 2014); Professor Hillegers from the Netherlands is cited in the ISBD report for the Dutch offspring study. Therefore, it can be said that the Task Force has limited international child psychiatry representation.

The Task Force did not mention or cite any of the international diagnosis comparison studies. It misrepresented the stark discrepancies by stating:

> The overall body of evidence supports the position that perceptions about marked international and developmental differences have been overstated, albeit that additional research on these topics is warranted. (p. 535)

The only real passing reference to international differences in diagnosis rates was this acknowledgement:

> [B]illing and services data show a marked increase in rates of diagnoses in the USA over a 20-year period (Blader and Carlson, 2007, Moreno et al., 2007). Differences in training, conceptualization of cases and insurance demands appear more of a factor (Dubicka et al., 2008). (p. 526)

We responded by reiterating the findings of Clacey, Goldacre and James (2015) of marked international discrepancies and added:

> The discrepancy in PBD diagnostic rates is several orders of magnitude greater than the trans-Atlantic discrepancy in schizophrenia diagnoses, which unsettled faith in psychiatric nosology prior to … DSM-III. Further research is required to inform the next edition of the DSM on BD in youth. (Parry, Allison & Bastiampillai 2018b, p. 2)

4.8.9.3.5 Task Force report mentions psychosocial factors

There was brief mention of psychosocial factors aggravating PBD psychopathology. In our debate article, we suggested these factors needed to be considered as potentially causative of mood lability and behavioural dysregulation and suggested:

> More systematic study should address lacunae in the PBD cohort studies … which either do not consider trauma/maltreatment, find much lower rates than usual community epidemiological prevalence, or, where a 16% rate of physical and sexual abuse was found (Axelson, Birmaher, Strober et al. 2011), do not discuss the finding. (Parry, Allison & Bastiampillai 2018b, p. 2)

4.8.9.3.6 Task Force report emphasises pharmacologic treatment

The Task Force concluded from the research evidence that: "SGAs [atypical antipsychotics] were effective" for PBD, but "youth are extra-sensitive to metabolic side-effects"; "mood-stabilizers less efficacious than in adults"; stimulants are "usually safe and efficacious" for "comorbid ADHD"; and "adjunctive nutritional interventions show promise" (p. 526).

We noted that the increase in atypical antipsychotic prescribing for children and young people poses "known health risks" and "the long-term benefits of SGAs [atypical antipsychotics] are unclear, as drug trials are generally short-term and none demonstrate that SGAs [atypical antipsychotics] reduce the risk of BD in later life" (Parry, Allison & Bastiampillai 2018b, p. 2).

4.8.9.4 The 21st Annual ISBD Conference, Sydney, Australia

The nine-article *CAMH* debate could have been a good place to complete this chronological history of the PBD phenomenon. However, debate over the nature of early onset of bipolar disorder in the paediatric age range is ongoing. This was apparent at the ISBD conference in Sydney that I attended from 20th to 23rd March, 2019.

We presented a poster (Parry, Allison & Bastiampillai 2019c; Appendix A36) that extended our re-analysis of the 12 original epidemiological studies of Van Meter, Moreira and Youngstrom (2011) to include the six extra epidemiological studies included in the PBD Task Force report (Goldstein et al. 2017). Table 2 from this poster is incorporated into Chapter 6.8.

The divergence in views on when and how bipolar disorder first manifests was quite apparent in the presentations. Most presentations that covered the early stages of bipolar disorder assumed the classical perspective. A keynote lecture by Professor Patrick McGorry (University of Melbourne) titled "Early intervention in bipolar and unipolar mood disorders: Time to push on an open door" was firmly in the classical perspective camp as to late adolescent/early adulthood age of onset of mania (McGorry 2019). McGorry highlighted the non-specific nature of psychiatric symptoms at earlier ages, as stated in the abstract of his lecture:

> Since psychiatric diagnosis is syndromal, and evolving comorbidity the rule from the earliest stages, a transdiagnostic approach to staging is essential. Creating an array of staging models for a range of DSM categories would not lead to progress. Anxiety and depression are symptoms and syndromes that emerge early in the course of most disorders and trajectories. Mania on the other hand is typically a syndrome that emerges later. It is crucial in that even at subthreshold level its appearance demands a change in therapeutics. (p. S9)

McGorry cautioned against premature use of antipsychotic medication until emergence of the classic syndrome.

A symposium titled: "Evolution of core features and manifestations of bipolar spectrum disorder" contained three presentations: 1) "Heritability of empirically derived patterns of mood and comorbid disorders and their longitudinal evolution in a community-based family study" by a research group from the NIMH (Merikangas et al. 2019); 2) "Predicting the onset of bipolar disorder in youth cohorts: Evidence from clinical and twin and sibling cohorts" by Australian researchers (Hickie et al. 2019); 3) "Antecedents and risk factors of mood disorders in a prospective high risk cohort study" by Swiss and Canadian researchers (Preisig et al. 2019). All of these speakers discussed bipolar disorder from the classical perspective of late adolescent/early adulthood-onset of first manic episodes.

In similar vein, Duffy, representing a group of Canadian and British authors, presented a review of the use of lithium the under-18 age range which they had recently published (Duffy, Heffer et al. 2018). Results for lithium in PBD cohorts from four US studies showed limited efficacy in contrast to lithium studies in older adolescents and adults with well-characterized mania. Duffy noted that this was yet another indicator that PBD was not the same syndrome

as classical bipolar disorder, as summarized in her 18th slide (Duffy et al. 2019) (A. Duffy, 2019, email, 25 March) (Figure 4.39).

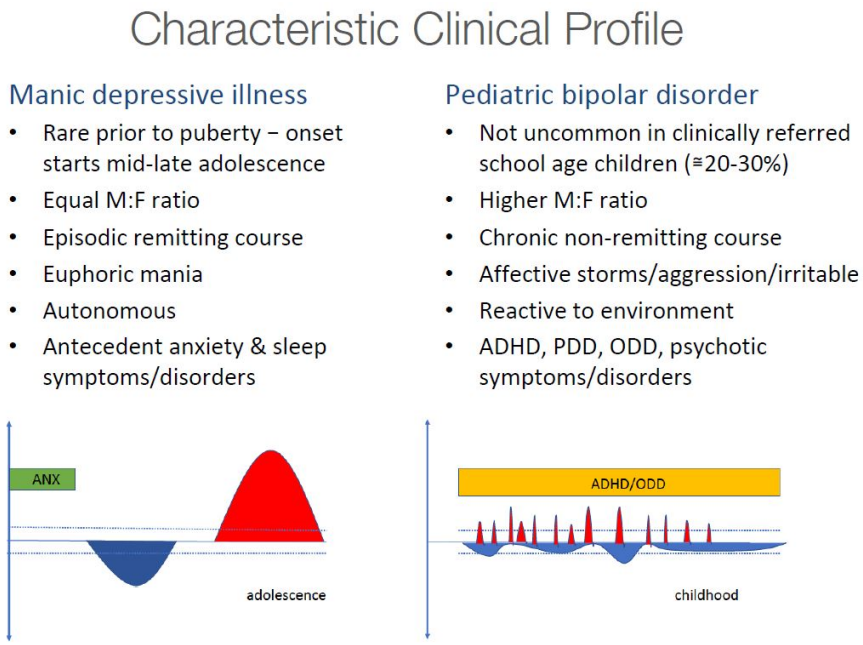

Figure 4.39: Slide 18 from Duffy et al. (2019) at 21st annual meeting of ISBD, Sydney. Reproduced with permission.

In contrast to the above, the "clinical case conference focused on mood disorders in children and adolescents" was in line with the PBD hypothesis (Goldstein et al. 2019). A case was presented of a 12-year-old boy whose mother had a history of depression, father alcohol abuse, the family had relocated to New York and the boy was exhibiting disruptive behaviour at his new school where he had no friends and unhappiness and oppositionality at home. On the basis of administered structured clinical interviews, the boy was described as having an "approximately 60%" risk of exhibiting bipolar disorder. This led to discussion where Australian colleagues in the audience suggested that contextual factors would be considered causative of the described phenomenology.

4.8.10 Competing views of ISBD Task Forces

This divergence in views on display at the ISBD conference, is reflected in the differing perspectives of the three task forces that deal with early-onset bipolar disorder. The Pediatric Bipolar Disorder Task Force chaired by Goldstein (Canada) and Youngstrom (US) conveys the PBD hypothesis; the Prospective Offspring Studies and Treatment Trials (POST) Task Force led by Scott (UK), Duffy (Canada), Mitchell (Australia) and Nolen (The Netherlands) research on

high-risk offspring; and the Staging Task Force led by Alda (Canada), Kapczinski (Canada) and Kupka (The Netherlands) examines the antecedent phenomenology of bipolar disorder (see https://www.isbd.org/active-task-forces). The latter two task forces operate within the classical model of bipolar disorder phenomenology whilst examining non-specific symptoms such as childhood anxiety disorders that may be early harbingers of later diagnosable bipolar disorder.

The diverging views persist through the ISBD website to the "clinician resources" section where a webinar titled "High-risk studies in bipolar disorder: Implications for earlier identification and intervention" (Duffy n.d.) is juxtaposed with "Mythbusting pediatric bipolar disorder: Reviewing the research to improve assessment and treatment" (Youngstrom n.d.). The "clinical notes" section has two downloadable pdfs with the same divergent perspectives: "ISBD Education Tip Sheet: Bipolar Disorder 101" that includes the statement: "It typically develops in late adolescence or early adulthood, although onset in childhood or in older adulthood may also occur" (ISBD Education n.d.-a, p. 1); and "ISBD Education Tip Sheet: Pediatric Bipolar Disorder" (ISBD Education n.d.-b) that includes statements such as:

> Bipolar disorder was once considered to be rare in adolescents and younger children, However, over the last decade, it has been increasingly recognized as a disorder of both children and adults ... Pediatric bipolar disorder is generally characterized by abrupt mood swings, periods of hyperactivity followed by lethargy, intense temper tantrums, frustration, and defiant behaviour. (pp. 1-2)

Within the ISBD website there is no discernible acknowledgment of these divergent views, rather they are presented as parallel perspectives on a crucial question as to when and how does bipolar disorder first occur?

Chapter 5 will summarise this history of the PBD phenomenon in light of other childhood psychiatric diagnostic epidemics, ADHD and ASD. It will also discuss how key research questions arising from an examination of the PBD epidemic were arrived at, to be explored in Part II.

CHAPTER 5. THE SPREAD OF THE US PBD EPIDEMIC: SUMMARY AND QUESTIONS

One of the primary goals of this thesis is to examine whether or not the PBD hypothesis is valid. To investigate this, Chapter 4 sought to chronicle the story of its spread, thereby providing a historical overview of the PBD phenomenon so far lacking in the literature, and address:

1. Why did it occur?
2. Iatrogenic consequences, and
3. Implications for medical ethics and psychiatric nosology

Before proceeding to the new research in Part II that sheds light on these questions, and discussion in Part III, one further question remains: 'has this happened before?'

5.1 Preceding epidemics: ASD and ADHD

PBD is not the only childhood psychiatric diagnostic epidemic to emerge from the US. Frances cites similar epidemics of ASD and ADHD in his article on the "epidemic of childhood bipolar disorder", and notes that the vagueness of ASD criteria and loosening of ADHD criteria in DSM-IV partially led to over-diagnosis of both (Frances 2010b, p. 1). The same can be said of PBD, which entered via the Bipolar-NOS window. A distinct difference with PBD is that it remained mostly confined to the US. Much has been written and could be written about the ASD and ADHD epidemics, however, a brief examination only of these other two epidemics follows, in order to establish commonalities and differences with PBD that in turn shed light on the above questions.

5.1.1 ASD as a diagnosis 'epidemic'

The prevalence of ASD has dramatically increased over recent decades. Most studies conducted from 1960 to 1980 show a prevalence ranging from 2 to 5 in 10,000. However, these studies assessed narrowly defined autistic disorder. Following the broadening of criteria in DSM-III-R (1987), rates of ASD surged (Wing & Potter 2002). Studies in the early 2000s reported prevalences ranging from 30 to 60 in 10,000, and a few years later had risen to 50

to 114 in 10,000 children (Fombonne 2009). The US Center for Disease Control (CDC) website reports their own ASD prevalence rates steadily rising from 67 per 10,000 children in the year 2000 to 66 in 2002, 80 in 2004, 90 in 2006, 113 in 2008, 147 in 2010, and 146 in 2012 (CDC 2017). There was a jump to 224 in 10,000 in 2014 after the CDC questionnaire to parents changed its wording (Zablotsky et al. 2015). The CDC now appears to be ignoring that result and quoting the 2012 rate as the latest (CDC 2017).

The highest rates were amongst white boys from higher SES demographics, which suggest subcultural perspectives influence diagnosis. Furthermore, the discounted result in 2014 reveals the vagaries of diagnosis by epidemiological survey.

In Australia, diagnostic up-coding to create an over-diagnosis epidemic of ASD has been driven not by need for health care reimbursement, but by welfare payments and schools' access to extra resources such as classroom assistants (O'Keeffe & Macaulay 2012; Basu & Parry 2013; Appendix A25).

5.1.2 **ADHD as a diagnosis 'epidemic'**

A similar pattern of outcomes in research varying according to methodology occurred with both ADHD and PBD. Unless rigorous co-informant and impairment criteria were applied, studies tended to produce high false positive rates. The real-world diagnostic rates, or what is termed 'administrative prevalence' rates of ADHD, have been escalating dramatically since the 1990s in many countries, as described in an article titled: "The impending globalization of ADHD: Notes on the expansion and growth of a medicalized disorder" (Conrad & Bergey 2014). The authors reviewed the literature to conclude that the ADHD diagnosis epidemic began in the US but, despite the stricter ICD-10 criteria for Hyperkinetic Disorder, has since spread to many countries.

A systematic review found that while diagnosis rates of ADHD have increased since the early 1990s in many countries, community epidemiological studies have shown no significant rise in rates (Polanczyk et al. 2014). However, the same authors posited a pooled prevalence rate of 5.29% in an earlier meta-analysis, although the rate (not stated) would have been less if based on concordance between informants, and impairment criteria were used. Two similarly low rates from Russia (1.3%) and Britain (1.4%) were cited based on conservative criteria,

while differing rates (3.7% to 8.9%) all from Puerto Rico were based on whether impairment criteria were applied or not (Polanczyk et al. 2007). These are similar issues to those involving PBD research, as discussed in Chapter 6.

Conrad and Bergey note a further marker of the spread of such epidemics can be found in the consumption of medication: In the 1990s the US consumed 90% of the world's methylphenidate, but despite further marked rises in diagnosis and prescribing, market share for methylphenidate fell to 75% by 2010 "as other countries adopted the treatment" (p. 32). The volume of ADHD medications increased 274% between 1993 and 2003 with the number of countries prescribing stimulants for ADHD increasing from 31 to 55. ADHD diagnoses increased in the UK from <1% in the 1990s to an NHS estimate of 2 – 5% by 2015 with a 35-fold rise in methylphenidate prescriptions between 1992 and 1997 and a doubling between 2003 and 2008. In Germany, prescriptions for stimulants rose from 10 million daily doses to 53 million daily doses between 1999 and 2008. In France, where psychiatry has a continuingly well-funded psychotherapeutic tradition, the proportion of children receiving stimulants for ADHD rose from 0.02% to 0.18% between 1997 and 2005. A similar emphasis on psychotherapies in Italy may have explained why only 0.8% of children with ADHD receive stimulants compared with 57%, 11% and 9% in US, UK and France respectively. In Brazil, although diagnosis and prescribing rates remain very low, there is a strong academic push for greater identification and treatment (Conrad & Bergey 2014).

Although beyond the scope of this thesis, there is a literature, both academic and investigative journalistic, that suggests pharmaceutical industry influence in the increasing diagnosis of ADHD. A study of the top 60 ADHD information websites showed that 37% were drug-company funded and significantly more likely to recommend medication (Mitchell & Read 2012). An interview with investigative journalist Alan Schwarz (who had penned 10 front page stories on the topic for *The New York Times*) in *Scientific American* was titled "Big Pharma's manufactured epidemic: the misdiagnosis of ADHD". Schwarz described the pharmaceutical industry's role as "a completely predictable one" (para. 6). He outlined the funding of research for marketing copy that was supplied to US parents via DTCA (Cook 2016). Therefore, parallels exist between the ADHD and PBD epidemic in the realm of pharmaceutical company influence.

In summing up their analysis of the spread of ADHD Conrad and Bergey (2014) identified:

> [F]ive key vehicles that appear to contribute to the globalization of ADHD: 1) the transnational pharmaceutical industry, 2) the increasing influence of biologically-oriented American psychiatry as a standard, 3) the adoption of DSM-IV criteria for diagnosing ADHD, 4) the Internet, including the availability of specific and simple screening checklists, and 5) ADHD advocacy groups (p. 36).

The relevance of these 'five key vehicles' to the emergence and adoption of the PBD hypothesis are quite apparent.

Two final comments on the parallel epidemics come from a doyen of the field, Jerome Kagan, Emeritus Professor of Psychology at Harvard University and a pioneer of developmental psychology with his work on infant temperament. He was interviewed by *Der Spiegel* saying of the ADHD epidemic:

> it is an invention. Every child who's not doing well in school is sent to see a pediatrician, and the pediatrician says: "It's ADHD; here's Ritalin." In fact, 90 percent of these 5.4 million kids don't have an abnormal dopamine metabolism. The problem is, if a drug is available to doctors, they'll make the corresponding diagnosis. (Grolle & Shafy 2012a; para. 13)

With regards to PBD, Kagan, in the same interview said:

> A group of doctors at Massachusetts General Hospital just started calling kids who had temper tantrums bipolar. They shouldn't have done that. But the drug companies loved it because drugs against bipolar disorders are expensive. That's how the trend was started. (Grolle & Shafy 2012b; para. 6)

Professor Kagan had come to the same conclusion as the US Senate Finance Committee's chairperson, Senator Grassley that the interplay between the pharmaceutical companies and some prominent academic departments of psychiatry was a critical factor in the PBD epidemic. This included the department of child and adolescent psychiatry at the MGH, affiliated to Kagan's own university, Harvard.

5.2 Implications for PBD

The five key vehicles that enabled the spread of the ADHD epidemic, according to Conrad and Bergey, are:

1. the transnational pharmaceutical industry,
2. the increasing influence of biologically-oriented American psychiatry as a standard,
3. the adoption of DSM-IV criteria for diagnosing ADHD,
4. the Internet, including the availability of specific and simple screening checklists, and
5. ADHD advocacy groups (p. 36).

In examining the contents of the overview, it is clear that all of these were present during the emergence of the PBD hypothesis, supporting the notion that it achieved 'epidemic' status.

5.2.1 Influence of the pharmaceutical industry

It is clear from the historical narrative, including the released internal industry documents, that the pharmaceutical industry wished to promote a widened bipolar spectrum to create a market for on-patent atypical antipsychotics. This will be further addressed in Part III.

5.2.2 Influence of bio-bio-bio psychiatry

An over-reliance on the biomedical model, instead of adhering to the more philosophically sound biopsychosocial model in a field such as mental health, is a widespread global problem that has been critiqued by numerous authors. There is a strong suggestion that this biomedical reductionism, or what has been termed the 'bio-bio-bio model' (McHugh, Romanoski & Treisman 2009) is a greater issue in the US than other countries, due to peculiarities of the US health system. The health care environment also appears to have affected psychiatric training in the US more than elsewhere. This will be explored in greater depth in Part III.

5.2.3 DSM criteria manipulated to fit the PBD hypothesis

Conrad and Bergey (2014) cite the incorporation of liberal criteria for ADHD into the DSM-IV as a reason for the 'ADHD epidemic', and the chair of the DSM-IV committee gave credence to this theory (Frances 2010b). As Frances pointed out though, the criteria for meeting the phenotypic versions of the PBD hypothesis lay outside of DSM criteria for bipolar disorder. However, it was through the NOS category that PBD could be considered as a DSM defined

diagnosis. From there, both the original PBD phenotypes managed to adopt the moniker of 'Bipolar-I disorder', even in major journals, for example: the 'narrow' phenotype (Geller et al. 2008; Chapter 4.8.2.15); the 'broad' phenotype, even well after the DSM-5 adoption of DMDD (Wozniak et al. 2017; Chapter 4.8.5.6).

Looking back over the near quarter-century of the PBD epidemic, it is apparent that the due process of academic debate and formal ratification of the PBD hypothesis as an assumed valid diagnostic entity by consensus of the different DSM committees was not followed. The Pittsburgh group are more in line with the DSM by using the term 'Bipolar-NOS', though the purported frequent progression to Bipolar-I and Bipolar-II disorder, which is at odds with the other longitudinal studies, raises concerns regarding whether a too liberal perspective is used in how symptoms are assessed (Carlson & Klein 2014).

5.2.4 Role of the internet and screening checklists

The online JBRF website that allowed quick diagnosis via a screening questionnaire of one's child and encouragement to seek a sympathetic doctor for confirmation is an example of this. Several websites offered information on PBD, particularly the websites of the key advocacy group CABF, and BPchildren.com.

5.2.5 Influence of advocacy group

The first CABF website could be directly accessed through the Papoloses' JBRF website. Renamed as the Balanced Mind Foundation, the influence of this 25,000-member strong well-meaning and motivated advocacy group cannot be understated. However, it was the influence of what I propose as a sixth vehicle, that of the media, that magnified the effects of the fourth and fifth vehicles.

5.2.6 Magnifying influence of the public media

The involvement of the public media further added to the 'perfect storm' of multiple factors that led to widespread public acceptance. In particular, best-selling books offered a simple answer to parents struggling with children's mood lability and disruptive behaviour. Influential TV shows such as the *Oprah Winfrey Show*, front page stories in *TIME* and *Newsweek*, and ubiquitous DTCA of 'mood stabilizers' to US consumers were critical.

Thus, according to Conrad and Bergey's key vehicles, PBD had the same drivers of an epidemic as ADHD.

5.2.7 Further factors in the PBD epidemic: Conflicts of interest and US health system

Additional factors emerged from the overview that encouraged psychiatrists and other physicians to favourably adopt the PBD hypothesis: the aforementioned conflict of interest driven literature and CME, but also the diagnostic up-coding pressures of the US health system. These, combined with the aforementioned five, may well have contributed to the rapid translation from research lab to clinical practice in the US, despite lack of DSM ratification. These will be examined further in Part III.

5.3 Next steps: novel research

Having now identified key themes that suggest that the PBD hypothesis was in fact a diagnosis epidemic, the critical 'next step' is to undertake specific research that will shed light on the key question of this thesis: is the PBD hypothesis valid?

The three specific questions that emerged from the comprehensive overview of the PBD epidemic are as follows:

5.3.1 Are the findings of the Van Meter et al. meta-analysis of epidemiological studies of bipolar disorders in youth valid?

A now widely cited community prevalence rate of 1.8% for PBD (Van Meter, Moreira & Youngstrom 2011) has been updated to 2.06% by the ISBD Task Force on PBD report (Goldstein et al. 2017). However, the original epidemiological studies contain few pre-pubertal children, and questions exist over methodology. The methodological aspects of Van Meter et al.'s meta-analysis and the findings of the original dozen epidemiological studies are examined in Chapter 6 and have been published (Parry, Allison & Bastiampillai 2018a; Appendix A31). Additionally, the six extra studies included by the ISBD Task Force are also examined (as per Parry, Allison & Bastiampillai 2019c; Appendix A36). The two extra epidemiological studies included in the updated meta-analysis (Van Meter, Moreira & Youngstrom 2019b) are also examined (Chapter 6.8.2.7; 6.8.2.8).

5.3.2 **How widely has the PBD hypothesis been accepted in the international literature?**

Discharge diagnosis rates of bipolar disorder in the child and adolescent age range have been published in recent years from the UK, Germany, Czech Republic, Australia, and NZ, as well as inpatient and outpatient rates from Denmark and the UK. These rates match older inpatient data from Denmark, Finland, the UK and NZ. All these rates are consistent with the classical perspective on bipolar disorder, and in line with Kraepelin's own findings of patients with manic-depressive insanity. Little has changed in clinical epidemiology outside the US, but the rates within the US exploded by several orders of magnitude since the emergence of the PBD hypothesis.

In fact, the disparities in discharge diagnosis rates for bipolar disorder between the US and Europe and Australasia are several orders of magnitude greater than the disparity between schizophrenia diagnosis rates half a century ago, which at the time caused dismay over the integrity of psychiatric nosology. However, the ISBD Task Force on PBD (Goldstein et al. 2017) claimed that:

> [P]erceptions about marked international (US vs elsewhere) and developmental (pediatric vs adult) differences have been overstated (p. 525)

The question then is to what extent is this discrepancy in diagnosis rates reflective of non-acceptance of the PBD hypothesis? By examining the international literature on PBD it may be possible to discover where the PBD hypothesis has spread and not spread to. This question is examined in a bibliometric review of PBD literature in Chapter 7, a more summarised version of which has recently been published (Parry, Allison & Bastiampillai 2019b; Appendix A35).

5.3.3 **Does the PBD research literature fail to consider context, specifically: attachment theory, developmental trauma and maltreatment factors?**

The side-lining of psychosocial therapies appears to have contributed to and been exacerbated by the PBD hypothesis and epidemic. This was commented on by many authors, including the head of the American Psychological Association committee to investigate

overprescribing of antipsychotics to children (Chapter 4.6.9). He described diagnostic up-coding practices and managed care insurance systems that favoured pharmacotherapy over non-drug interventions. Rarely did the PBD research appear to explore common child psychiatric territory such as contextual family dynamic, parenting, attachment, maltreatment and trauma factors. To assess whether this was in fact the case a bibliometric review of PBD literature was undertaken and the results are discussed in Chapter 8.

5.4 **Summary**

These three research questions are addressed in the 3 chapters in Part II, each of which have related publications (Appendices A31, A35, A19) and the implications are elaborated in Part III, the Discussion section.

To briefly summarise: 1) A narrative analysis of all 19 studies now cited by Van Meter, Moreira and Youngstrom (2019b) in their most recent updated meta-analysis provides no evidence to support a common pre-adolescent childhood-onset for hypomania/mania; 2) a bibliometric review of a citation tree of PBD-related articles reveals the PBD hypothesis to mostly have remained confined to several US academic institutions with limited spread to a number of southern European and Latin American institutions as well as South Korea; 3) a bibliometric review of a large body of PBD literature indicates that attachment theory, developmental trauma and maltreatment factors are mostly not mentioned, thereby undermining the validity of the PBD construct for not considering alternative explanations for the mood lability and irritability symptoms that the PBD hypothesis is constructed upon.

The implications of such a long-running epidemic of misdiagnosis of young children are profound. The PBD epidemic brought iatrogenic consequences of adverse effects of psychotropic medication including mortality, labelling effects on children and their families, and limited recognition of alternative diagnoses or contextual factors such as childhood maltreatment.

That the field of psychiatric nosology was unable to provide clearer guidance to researchers and clinicians warrants a re-appraisal of the factors that influence the making of psychiatric diagnoses. These factors are examined in Part III and include: the decontextualized model for psychiatric nosology adopted in DSM-III in 1980; a divergence from the biopsychosocial model

to what has been termed a ‘bio-bio-bio’ model; the influence of the pharmaceutical industry on research, training, clinical practice, DSM committees and public awareness; the tendency in human society towards denial of childhood maltreatment; and particularly in the US, a health care system that encourages ‘diagnostic upcoding’ to more severe diagnostic labels in order to access services and tends to then favour pharmacotherapy over talking therapies.

PART II – NOVEL RESEARCH

Part II contains three separate pieces of research. The first (Chapter 6) is a re-analysis of the widely cited meta-analysis of Van Meter, Moreira and Youngstrom (2011) (Chapter 4.27.6) and of the recent updated meta-analysis (Van Meter, Moreira & Youngstrom 2019b). The second (Chapter 7) involves a citation-tree analysis to compare perspectives on the PBD hypothesis within the US and in other countries. The third (Chapter 8) examines the existence of attachment, maltreatment and trauma concepts in the PBD literature.

Both chapters 7 and 8 are bibliometric literature reviews. The Oxford English Dictionary defines “bibliometrics” as the “application of mathematical and statistical analysis to bibliography; the statistical analysis of books, articles, or other publications” (accessed at oed.com).

CHAPTER 6. THE PREVALENCE OF BIPOLAR DISORDER IN CHILDHOOD AND ADOLESCENCE: A RE-EXAMINATION OF VAN METER, MOREIRA & YOUNGSTROM, 2011 & 2019B.[1]

6.1 Introduction

The meta-analysis by Van Meter, Moreira and Youngstrom (2011) claimed that the prevalence of PBD was similar to adults at 1.8% with no difference between the US and other countries. This widely cited prevalence figure continues to be used as something of a 'cornerstone' of the PBD hypothesis.

The authors had noted that:

> The United States is widely perceived as having higher rates of pediatric bipolar disorder than other countries, but the cause of this disparity has not been explored. Differences in international rates of disorder may be due to the diagnostic criteria employed or to other clinical disparities such as the way in which different symptoms are interpreted (Parry & Allison, 2008; Dubicka et al., 2008). (p. 1250)

In fact, the causes of the disparity had been explored in both those articles they cited: Parry and Allison (2008; Appendix A2) listed diagnostic upcoding pressures and pharmaceutical company influences and Dubicka et al. (2008) noted differences in psychiatric training and pharmaceutical marketing factors in the US (Chapter 4.8.6.6). Additionally, the Hastings Center workshop had examined these factors in the US that drove the epidemic (Parens & Johnstone 2010; Chapter 4.8.2.23). Nonetheless, there was limited literature in 2011 on the vast discrepancy in PBD diagnosis rates between the US and other nations. The authors stated:

> [C]onclusions cannot currently be drawn regarding alleged increases in pediatric bipolar disorder rates or differences in rates of pediatric bipolar disorder internationally. (p. 1250)

[1] *This chapter includes passages that have been published (Parry et al. 2018a; Appendix A31).*

It is of obvious concern for US child psychiatrists and its health system if diagnostic rates of PBD are far higher in the US than elsewhere.

Van Meter et al. located 12 epidemiological studies, 6 US and 6 non-US, which taken together provided a reported subject pool of *n* = 16,222. Their meta-analysis of these dozen studies claimed to show an "overall rate of bipolar disorder of 1.8%" and "there was no significant difference in the mean rates between US and non-US studies, but the US studies had a wider range of rates" (p. 1250). Van Meter et al. expanded upon this in the discussion:

> Results do not align with the theory that rates of bipolar disorder are higher in the United States than in other countries. There is a perception that pediatric bipolar disorder is an "American problem", but present findings indicate no difference in the rates in the United States versus the rest of the world. (p. 1254)

Figure 6.1 is 'Figure 2' from Van Meter, Moreira and Youngstrom (2011). It shows the 12 studies and summarises the stated outcomes of the meta-analysis, including the claimed global prevalence rate of 1.8%.

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Image description: A graph with percentage on y axis and each of 12 epidemiological surveys on x axis comparing weighted prevalence rates, titled 'Weighted Bipolar Prevalence Rates Sorted by Year of Data Collection and Denoting US Versus International Samples'.

Figure 6.1: Weighted Bipolar Prevalence Rates Sorted by Year of Data Collection and Denoting US versus International Samples (Van Meter, Moreira & Youngstrom 2011, p. 1253)

This study was published in *The Journal of Clinical Psychiatry.* The "Clinical Points" highlighted in the published article were:

1. The prevalence of pediatric bipolar disorder is similar to current prevalence estimates of bipolar disorder in adults;
2. The prevalence of pediatric bipolar disorder is not different in the United States, relative to other countries;
3. The prevalence of pediatric bipolar disorder is not increasing over time in the community, even as it is being diagnosed more commonly in clinical settings.

6.1.1 Van Meter et al. (2011) cited to support PBD hypothesis

This meta-analysis has been widely cited: As of 24 June 2019, there were citations in 72 articles in *PubMed*, 168 in *Web of Science*, 191 articles in *Scopus* and 304 in *Google Scholar* databases. Perhaps the most prominent use of the 1.8% finding is not a citation as such, but a direct quotation in the DSM-5 (APA 2013) itself:

> The prevalence rate of pediatric bipolar II disorder is difficult to establish. DSM-IV bipolar I, bipolar II, and bipolar disorder not otherwise specified yield a combined prevalence rate of 1.8% in U.S. and non-U.S. community samples, with higher rates (2.7% inclusive) in youths age 12 years or older. (p. 136)

Incongruously, the very next paragraph in the DSM-5 states: "Although bipolar II disorder can begin in late adolescence and throughout adulthood, average age of onset is the mid-20s" (p. 136).

National and international treatment guidelines have cited Van Meter et al. for the 1.8% figure in bipolar disorder documents. The Canadian Network for Mood and Anxiety Disorders (CANMAT) management guidelines (Yatham et al. 2013), developed in collaboration with the ISBD, state:

> Based on a meta-analysis of 12 epidemiological studies in patients between the ages of seven and 21 years (n = 16,222), the overall prevalence of BD was 1.8% [Van Meter et al., 2011]. Of note, rates of BD in these epidemiologic studies did not increase over time and did not differ for studies within versus outside of the USA. (p. 20)

The British Association for Psychopharmacology treatment guidelines (Goodwin GM et al. 2016) also refer to the study, and state:

> There is some consistency in reports of the prevalence of bipolar diagnoses in young people in different countries. The average rate for age 7–21 years was 1.8% (95% CI, 1.1–3.0%). This is probably higher than appreciated (Van Meter et al., 2011). (p. 513)

The open access *IACAPAP 2012 e-textbook* chapter on bipolar disorder (Diler & Birmaher 2012), was published in conjunction with the 2012 IACAPAP World Congress and recently updated (Diler & Birmaher 2019). It is potentially very influential, as noted in the textbook's updated foreword (Omigbodun 2015) the IACAPAP *e-Textbook* is designed "for the purpose of education and training" of child and adolescent mental health professionals in "developing countries" (p. xviii). The chapter is strongly supportive of the PBD hypothesis, the authors being from the Pittsburgh group. The meta-analysis was prominently quoted in both the original 2012 edition and the current 2019 edition of chapter 'E2 Bipolar Disorder' (Diler & Birmaher 2019):

> A recent meta-analysis about the epidemiology of BD in youth around the world – enrolling 16,222 youth between the ages of 7 and 21 years during a period from 1985 to 2007 – reported that the overall rate of BD was 1.8% (95% CI, 1.1%–3.0%) (Van Meter et al., 2011). (Diler & Birmaher 2012, Introduction; Diler & Birmaher 2019, chapter E2, p. 5)

> Many clinicians around the world still remain skeptical about persistent non-episodic manic symptoms, ultra-rapid mood cycling, and BD diagnosis in preschool children (Diler, 2007). However, a recent meta-analysis of international epidemiological studies suggests that rates of BD in youth are similar in US and non-US studies (Van Meter, 2011). (Diler & Birmaher 2012, Conclusion; Diler & Birmaher 2019, chapter E2, p. 26)

Youngstrom, who co-authored the meta-analysis, has cited it to support the idea that prevalence rates of PBD are equivalent internationally, but higher than clinical rates especially outside the US. For example, in an Israeli psychiatric journal (Youngstrom et al. 2012):

> There are now several thousand peer-reviewed articles describing and validating pediatric bipolar disorder, drawn from dozens of independent research groups around the world (Youngstrom et al., 2008). A recent meta-analysis of epidemiological studies found that ~2% of children and adolescents in the community - not clinics - meet criteria for bipolar spectrum diagnoses (Van Meter et al., 2011), with equal rates in the U.S.A. versus the rest of the world. (p. 15)

The meta-analysis was also cited in a press release by the pharmaceutical company Sunovion, in an FDA application for use of the atypical antipsychotic lurasidone "for the treatment of depressive symptoms associated with Bipolar I disorder in children and adolescents (10 to 17 years of age)" (Coppola 2017; para. 7).

However, my initial reading of Van Meter, Moreira and Youngstrom (2011), suggested the 12 epidemiological surveys did not lead to such a high prevalence rate, and I commented on the heterogeneity of the studies at the APA symposium (Parry 2013).

The meta-analysis was also critiqued by Carlson and Klein (2014) (Chapter 4.8.2.35) who noted the following three points: the epidemiological surveys mainly studied adolescents and did not focus on the pre-pubertal age range in question; the meta-analysis combined parent and youth report data even though there was frequently complete disagreement; and it did not include follow-up data to validate or invalidate a bipolar spectrum disorder diagnosis. Their critique stated:

> A closer look at the articles in the meta-analysis, however, reveals that very few studies provide satisfying information, and those that do have found lower rates. The study by Kim-Cohen et al. (2003), done on the NZ Dunedin cohort, was included in error; it did not measure mania in youth under age 18. In the Netherlands study (Verhulst et al. 1997), the ≈2% rate was achieved by adding the parent rate (1.1%) and the teen rate (0.9%). As the authors noted, there was very little overlap in symptom reports, and the authors themselves were quite sceptical of their results. Stringaris and colleagues (2010) required convergence between parent and child reports to diagnose bipolar disorder because they found a very low kappa (0.02%) between parent and child. Doing so yielded a rate of mania of 0.1%. In a much smaller community study using parent information to corroborate child data, Carlson and Kashani (1988) also found low rates (0.7%). Although the

> Methods for the Epidemiology of Child and Adolescent Mental Disorders study (Goodman et al. 1998) was cited as having a rate of mania of 1.3%, symptoms from either a parent or child were used. Reliability for mania was never examined because the condition was too rare. Rates were likely much lower than 1.3% - closer to 0.4% to 0.6% when convergence reports were required (P. Fisher, personal communication). Nevertheless, rates are variable even when using a single informant. Using only teen reports, the lifetime rate for mania was found to be 0.1% in the Oregon Adolescent Depression Project (Lewinsohn et al. 1995) and 1.7% in the National Comorbidity Survey-Adolescents (Merikangas et al. 2012). (p. 536)

However, Carlson and Klein (2014)'s critique was half a page within a 23-page article and Van Meter, Moreira and Youngstrom (2011)'s findings have continued to be widely cited, while Carlson and Klein's rebuttal has not. Google Scholar reports 37 citations for Carlson and Klein (2014) as of 24 June 2019. Apart from our two citing articles (Parry, Allison & Bastiampillai 2018a, 2019b; Appendices A31, A35), only one of these citing articles, which actually involved two of the meta-analysis authors, acknowledged the informant problem of "shared source variance", but still did not mention the critique of the prevalence figure (Youngstrom et al., 2015, p. 128).

Since reading of the individual original studies suggested even further differences to those outlined by Carlson and Klein, my colleagues, Stephen Allison and Tarun Bastiampillai, and I published in *Child and Adolescent Mental Health* a re-examination of the original 12 surveys and came to a conclusion in keeping with the classical and internationally accepted perspective of age at onset of bipolar disorder (Parry, Allison & Bastiampillai 2018a; Appendix A31). Our findings are elaborated on below.

6.2 Method

6.2.1 Method Part A

Firstly, the original 12 epidemiological surveys were investigated to determine if they adequately satisfied homogeneity requirements to warrant a statistical meta-analysis, as was performed by Van Meter, Moreira and Youngstrom (2011).

6.2.2 **Method Part B**

Nonetheless, Van Meter and colleagues had selected what they believed the best epidemiological data for community prevalence rates of bipolar disorder in youth: for the second part of this study, each of the 12 studies (six from the US; six from other countries) were re-examined using a qualitative analysis approach.

6.3 **Results**

To facilitate understanding of the detailed results Figure 6.2 below, based on the previously published paper (Parry, Allison & Bastiampillai 2018a), provides a summary of each of the studies, the methodology used, and the key findings for each.

6.4 **Part A Results: Examining methodology**

6.4.1 **The 12 surveys were unsuitable for statistical meta-analysis**

The dozen original epidemiological studies had marked heterogeneity as a group. Key differences were:

- The results of the individual surveys varied widely in prevalence results.
- Differing diagnoses on the bipolar spectrum, sometimes including cyclothymia, were used.
- The surveys covered years where different editions of the DSM were used.
- Most surveys predated the emergence of the PBD hypothesis, but some did not, and this appears to have influenced some findings.
- Differing survey instruments were used, and assessment periods varied from point prevalence to 3-month, 6-month, 12-month, and lifetime, adding further variation.
- Impairment criteria were only sometimes applied.
- Age ranges of the subjects varied. Most subjects were in the adolescent to even young adult age range. Few pre-pubertal children were surveyed.
- The surveys used different informants, and ways of combining informant data.

Given this lack of homogeneity of the 12 studies, the suitability of this collection of studies for meta-analysis is highly debatable. The Cochrane Handbook for Systematic Reviews of Interventions (Deeks, Higgins & Altmann 2011) notes the criticisms of meta-analyses include:

> A common criticism of meta-analyses is that they 'combine apples with oranges'. If studies are clinically diverse then a meta-analysis may be meaningless, and genuine differences in effects may be obscured … Often it is nonsensical to combine all included studies in a single meta-analysis. (Part 2, 9.1.4)

Most of the above variations are listed in Figure 6.2 and expanded in the next section.

Source Subjects	Location Year completed Criteria	Instrument Prevalence period Age	Critique	Van Meter meta-analysis	BD-I %	Total Bipolar Spectrum %	
Non-US studies (Van Meter et al. total)				(1.9%)			
Kim-Cohen et al, 2003 N = 973	New Zealand 1985 DSM-III	DISC 12 mth	Did not ask about mania til after age 18	1.8%	0% or N/A	0% or N/A	
Verhulst et al, 1997 N = 780	The Netherlands 1993 DSM-III-R	DISC 6 mth 13-18 yrs	Added parent and child information despite complete informant disagreement	2.8%	1.9% added 0% agreement	2.8% added 0% agreement	
Canals et al, 1997 N = 290	Spain 1994 ICD-10, DSM-IV	SCAN Point 17-18 yrs	Adolescent only informant Nil cases by DSM criteria, Van Meter et al chose hypomania cases by ICD criteria only	2.4%	0% DSM 0% ICD	0% DSM 2.4% ICD	
Lynch et al, 2006 N = 723	Republic of Ireland 2002 DSM-IV	K-SADS Lifetime 12-15 yrs	Parent and adolescent agreement required or clinician judgment if non agreement	0%	0%	0%	
Benjet et al, 2009 N = 3,005	Mexico City 2005 DSM-IV	CIDI 12 mth 12-17 yrs	Adolescent only informant BD-I % deduced from Benjet et al text	2.5%	2.05%	2.5%	
Stringaris et al, 2010 N = 5,326	United Kingdom 2007 DSM-IV	DAWBA Lifetime 8-19 yrs	Child/adolescent and parent informants with minimal correlation: *kappa* 0.02 Authors conclude BD-NOS *not* on same bipolar spectrum with BD-I & BD-II	1.2%		BD-I plus BD-II	If include BD-NOS with full age range
			All ages 8-19 years		Part of 0.1% added or 0.04% agreement	0.1% added 0.04% agreement	2.6% added 0.04% agreement
			8-15 years		Part of 0.03% added or 0% agreement	0.03% added 0% agreement	
			16-19 years		Part of 0.4% added or 0.1% agreement	0.4% added 0.1% agreement	
US studies (Van Meter et al. total)				(1.7%)			
Kashani et al, 1987 N = 150	Missouri 1986 DSM-III	DICA Lifetime 14-16 yrs	One girl diagnosed by parent and adolescent agreement and consideration of impairment criteria. Carlson & Kashani (1988)* reviewed data and concluded three adolescents had cyclothymia	0.7%	0.7% 0%*	0.7% 2%* (all cyclothymia)	
Lewinsohn et al, 1995 N = 1,709	Oregon 1988 DSM-III-R/DSM-IV	K-SADS Lifetime 14-18 yrs	Adolescent only informant Hypomania and cyclothymia reported BD-NOS cases of 5.7% did not continue as bipolar cases on young adult followup	6.7%	0.1%	1.0%	
Costello et al, 1996 N = 1,015	Nth Carolina 1994 DSM-III-R	CAPA 3 mth 9-13 yrs	Parent and child/adolescent informant added	0.1%	0%	0.1%	
Andrade et al, 2006 N = 619	Hawaii 1994 DSM-III-R	DISC Lifetime 13-21 yrs	Adolescent only informant Do not distinguish what % is mania v hypomania	1.5%	Part of 1.4%	"Mania-hypomania" 1.4%	
Gould et al, 1998 N = 1,285	USA 1996 DSM-III-R	DISC 6 mth 9-17 yrs	Parent and child/adolescent reports added Possibly "mania" includes "hypomania"	1.3%	Possibly less than 1.2%	1.2%	
Kessler et al, 2009 N = 347	USA 2003 DSM-IV	K-SADS, CIDI Lifetime 13-17 yrs	Adolescent only informant	6.3% (K-SADS)	0.5% (K-SADS) 1.0% (CIDI)	6.2% (K-SADS) 6.6% (CIDI)	

Figure 6.2: The 12 epidemiological studies (Parry, Allison & Bastiampillai 2018a, pp. 16-17). Reproduced with permission.

6.4.2 **Prevalence rates**

A critical concern regarding the six US studies relates to the large variation in methods and prevalence rates found. This appears to have occurred because some studies took a traditional conservative perspective on bipolar disorder, for example, the early Great Smoky Mountains study (Costello et al. 1996); while other studies adopted a liberal frame for diagnosing bipolar disorder, for example, (Kessler et al. 2009) that was conducted during the midst of the US PBD epidemic. This had the effect of reducing the overall rate to below what PBD proponents predicted. The non-US studies were from the Netherlands, the UK, Spain, Mexico, Ireland, and NZ. The British, Irish and NZ studies appear to have involved a more conservative classical perspective, while the Spanish and Mexican may have been more liberal in perspective. The Dutch study's prevalence rate varied enormously depending on how informant data was handled.

Van Meter at al. alluded to heterogeneity of the studies when they acknowledged that "differences in diagnostic criteria were a main driver of different rates across studies" (p. 1250). Such very wide prevalence rates from 0% to 6.7%, across the original studies, makes statistical meta-analysis difficult to interpret, if not meaningless. It is this lack of homogeneity that is critically significant, and yet was lost in the "Clinical Points" and wider academic literature message.

6.4.3 **Diagnostic criteria**

A second concern relates to the diagnostic criteria used. Of the six US studies, two used 'broad criteria' and four used 'narrow criteria'. This was Van Meter et al.'s description, meaning liberal or conservative perspective on the boundaries of bipolar disorder, and mostly unrelated to the 'broad' and 'narrow' phenotypes of the PBD hypothesis. It also related as to whether Bipolar-I, Bipolar-II, Bipolar-NOS, a combined bipolar spectrum disorder, plus or minus cyclothymia, or some combination thereof, were in the scope of each survey. Of the six non-US studies, five used broad criteria and only one used narrow criteria according to Van Meter, Moreira and Youngstrom (2011). The rate of broad or "homogenous bipolar disorder" as described by Van Meter et al. found in the two 'broad' US studies was 6.7%, whereas in the five 'broad' non-US studies it was 2.4% (p. 1253). But this disparity, whilst clearly of high significance regarding the question of international differences in rates of

diagnosis, was only reported in a flow chart of the meta-analysis (Van Meter, Moreira & Youngstrom 2011; p. 1253) and not described in the text or abstract. It is clear that widely differing criteria had led to widely different results.

6.4.4 **Instrumentation**

Diagnostic instrumentation used was the source of further differences between the studies. Seven different instruments (Figure 6.2) were used across the 12 surveys. This also leads to the 'apples and oranges' comparison problem noted by the Cochrane Handbook above. Differing instruments that have not been through the same external validation process are likely to provide different diagnostic and therefore prevalence results.

Of further concern, even when the same instrument was used by differing studies, markedly different results could be found too. Both of the 'broad' (as defined by Van Meter et al.) diagnostic methodology US studies (Lewinsohn, Klein & Seeley 1995; Kessler et al. 2009) used the K-SADS, as did the 'broad' methodology Irish study (Lynch et al. 2006). The K-SADS (Chapter 4.8.3.4) has been much used in diagnosing PBD, for example, in the WUSL modified version of it, the WASH-U-K-SADS. Van Meter et al. stated that "the 3 studies using the K-SADS included the lowest and 2 highest estimates" (p. 1253). In fact, the lowest estimate occurred in the Irish study that found 0% bipolar cases in a sample of seven hundred twenty-three 12 – 15-year-olds. The two higher estimates with the K-SADS were the US studies that found rates of 6.7% in one thousand seven hundred nine 14 – 18-year-olds (Lewinsohn, Klein & Seeley 1995) and 6.3% in three hundred forty-seven 13 – 17-year-olds (Kessler et al. 2009). Such extremely divergent results suggest the methodologies and perspectives of the research groups need to be studied individually to derive meaning, rather than mathematically attempting to combine such results via a statistical meta-analysis.

Use of impairment criteria to define caseness was not undertaken in several of the studies, but if it was, as in Kashani et al. (1987), and then further applied in a more detailed review of the same data by Carlson and Kashani (1988), the subject who had been classed as having Bipolar-I disorder reverted to cyclothymia, though Carlson and Kashani in their review did identify two more cyclothymic subjects. When impairment criteria were carefully applied in the British survey (Stringaris, Santosh et al. 2010), nuanced differences were found between parental and youth report and in whether Bipolar-NOS cases were truly impaired or their

social impairment was related to comorbidities. This illustrated the importance of detail in such epidemiological surveys.

6.4.5 Time frame of studies

Another set of concerns lies within the data collection years for all the US studies. With the sole exception of Kessler et al. (2009), the study data was collected between 1986 and 1996. This particular time frame should effectively have allowed indications of US views on bipolar disorder prevalence to be made without the influence of the PBD hypothesis, in five of the studies. However, the outlier with the highest rate was Lewinsohn, Klein and Seeley (1995) who collected their data in 1988, and it is a retrospective analysis of that data that gives the high rate of "broad spectrum" bipolar disorder of 6.7%. Although Lewinsohn et al. was published too early to cite PBD hypothesis research groups, they favourably cited Akiskal and Mallya's (1987) article "Criteria for the 'soft' bipolar spectrum" to say "milder conditions may be the most common forms of bipolar disorder" (p. 454), reflecting the 'soft bipolarity' ideas that preceded the PBD era. What is particularly interesting is that the follow-up study (Lewinsohn, Klein & Seeley 2000) found that the broad phenotype of mood irritability did not progress to adult bipolar disorder**.** This suggests the initial diagnosis of PBD was incorrect, or, from the perspective of a DSM-5 era, that adolescents initially diagnosed may have been better categorised as exhibiting DMDD. Kessler's 2009 study, conducted during the PBD era, has the other unusually high prevalence rate, and presumably reflects the influence of the PBD hypothesis upon the researchers.

In contrast to the US studies, three of the non-US studies had data collected before 1995, the other three studies collected data in 2002 (Lynch et al. 2006), 2005 (Benjet et al. 2009) and 2007 (Stringaris & Goodman 2009). Consequently, it may have been expected that the literature of the PBD hypothesis era may have fostered a broader bipolar spectrum perspective in the Irish, Mexican, and British studies. However, the Irish study did not cite any PBD hypothesis literature, though it did cite three earlier epidemiological studies of the twelve used by Van Meter et al. (Costello et al. 1996; Kashani et al. 1987; Verhulst et al. 1997). The Mexican study also did not cite any PBD hypothesis literature, but did cite the Costello et al. Great Smoky Mountains study as Lynch et al. had. So, unlike Kessler et al. in the US, the Irish and Mexican studies showed no awareness of the PBD hypothesis. Nonetheless, the

Mexican study, with a large sample of 3,005 adolescents and a high prevalence result of 2.5%, would have boosted the non-US figure in the weighted prevalences in the meta-analysis (Figure 6.2).

In contrast, the British study (Stringaris, Santosh et al. 2010) had cited a range of PBD hypothesis articles of both pro-PBD and classical perspectives and indicated a thorough awareness of the PBD controversy. In methodological terms, this was perhaps the most rigorous study for examining community prevalence of bipolar disorder during the PBD hypothesis era. Stringaris, Santosh et al. (2010) in 2007 found a 1.2% rate of bipolar disorder, which was predominantly BD-NOS. This study was the single non-US 'narrow' criteria study as defined by Van Meter, Moreira and Youngstrom (2011). It had the largest sample size (5,326) of all, the prevalence rate found of 1.2% effectively kept the combined mean rate of apparent PBD high for the non-US studies. Conversely the relatively large (1,015 subjects) US Great Smoky Mountains study (Costello et al. 1996), using conservative diagnostic methodology for bipolar disorder, found instead a 0.1% rate of bipolar disorder and effectively suppressed the overall mean for the US studies. These mathematical considerations may have led to the even prevalence rate between US and non-US studies that became a key message of the Van Meter et al. article. However, as described below, Stringaris, Santosh et al. (2010) were aware and sceptical of the PBD hypothesis and argue for a rate of 0.1% from the British survey, akin to the Great Smoky Mountains rate. If so, then the non-US combined results would have been significantly lower than the US results.

In summary, the PBD hypothesis, including Akiskal's forerunner ideas, appears to have possibly affected the high rates for two US studies (Lewinsohn, Klein & Seeley 1995; Kessler et al. 2009) and have been understood and dealt with sceptically by the British study (Stringaris, Santosh et al. 2010). However, it did not affect the earlier US studies, nor appear to directly impact the other non-US studies.

6.4.6 **All 12 studies almost solely surveys of adolescents**

A further highly significant issue with the meta-analysis is that the studies were predominantly of adolescent populations and not of pre-pubertal children per se. Just four of the twelve studies included children under age 12 (listed first in italics in the following summary). The age ranges were: *7-18, 8-19, 9-13, 11-15*, 12-15, 12-17, 13-17, 13-18, 13-21,

14-16, 14-18, 17-18. This reflects a longstanding problem with all PBD research, critiqued as far back as 1960 by Anthony and Scott who argued for clarification of pubertal status in research (Chapter 2.2). Pre-school, pre-pubertal, adolescent, and adult neurodevelopment is so different that precision regarding ages in research would assist greatly. The mixture of age ranges across the dozen surveys is therefore problematic, particularly the low numbers of pre-pubertal children. Consequently, the meta-analysis fails to address the main controversy of the PBD hypothesis, that is, the diagnosis of mania in pre-pubertal children. Van Meter et al. did acknowledge this profound limitation:

> Although, historically, bipolar disorder has been considered an adult disorder, its presence in prepubescent children is now widely accepted. Unfortunately, the ages included in most of the studies reported here reflect this now-outdated perception. As such, the results may appear to be more representative of the rate of bipolar disorder in adolescents. Studies with a younger minimum age had lower prevalence estimates, those with more adolescents tended to have higher prevalence estimates.
>
> … Diagnoses in prepubescent children are particularly controversial; future studies including youth as young as preschool-aged, will provide a more complete picture of the rate of bipolar disorder across development. (p. 1254)
>
> The fact few studies included youth under the age of 12 years limits our knowledge of the rate of bipolar disorder in children … no study stratified its sample by pubertal status. (p. 1255)

These were important limitations, well described by Van Meter et al. Nonetheless, they declared their allegiance to the pre-pubertal PBD hypothesis perspective, saying "its presence in prepubescent children is now widely accepted" (p. 1254). The use of the very term PBD and "pediatric bipolar spectrum disorders" (p. 1251), as well as the now widely cited "7 – 21-years" age range, combine to give the impression that the 12 epidemiological surveys did detect pre-pubertal cases in reasonable numbers. The way the data was reported in the DSM-5 (as above) strongly gives this impression: citing 1.8% for the full age range and then 2.7% for "youth 12 years and older" (p. 136), gives an impression of younger cases. In fact, the 2.7% figure applies only to the six studies that did not have 12-year-olds or younger in them (p. 1252): at an individual study level, a detailed interpretation of each of the studies fails to

confirm a single clear-cut pre-pubertal case. This vitally important negative finding is obscured in the meta-analysis and the cycles of citation.

6.4.7 Informant variance

The issue of multiple informants for making psychiatric diagnoses in epidemiological research in adolescents is complex. Generally, agreement of parent and adolescent reports is desirable and improves accuracy of diagnosis (Jensen et al. 1999; Rescorla et al. 2017) but the issue is not completely straightforward and varies in complex ways depending on informants, instruments and disorders (De Los Reyes et al. 2015). Parent and youth agreement reduces false positives, but at risk of some false negatives (Polanczyk et al. 2015). Parent/Caregiver report has been claimed to be more accurate than just adolescent report in diagnosing youth with PBD (Youngstrom et al. 2015). Adolescent-only reports, without parent report confirmation, may have inflated the bipolar spectrum rates in the Spanish, Mexican and two of the US Studies of Lewinsohn, Klein and Seeley (1995) and Kessler et al. (2009).

The discrepancy in informant data is profound and was borne out in the Dutch and British surveys: Van Meter, Moreira and Youngstrom (2011) chose a rate of 2.8% by summation of adolescent and parent responses in a Dutch survey: however, the rate fell to 0% if requiring concordance of adolescent and parent responses. The careful methodology of the British study (Stringaris, Santosh et al. 2010) clearly illustrated this importance of informant concordance on the ultimate results, with a low *kappa*, and marked fall in prevalence rates with informant concordance, e.g. from 2.6% to 0.04% for total bipolar spectrum for 8 – 15-year-olds (Figure 6.2).

If this approach is applied, and the DSM not ICD criteria used in the Spanish survey, then it could be argued that four of the non-US studies show 0% rates and one shows 0.04% for total bipolar spectrum, leaving the Mexican adolescent informant survey as an outlier with 2.5%.

6.5 Part B Results: Narrative analysis of each survey

The six US studies are examined first, then the six non-US studies. All of the data referred to below is summarised in Figure 6.2.

6.5.1 The six non-US studies

6.5.1.1 Kim-Cohen et al. 2003 (conducted 1985, NZ).

Kim-Cohen et al.'s (2003) study is a retrospective analysis into childhood psychopathology for adults who were by that time aged 26. The authors note that the accuracy of retrospective reporting is often suspect, especially timing the age of onset, but this study had the advantage of juvenile prospective data for comparison in a 'follow-back' analysis.

This NZ study examined 973 individuals, 11 – 15-year-olds from the Dunedin longitudinal birth cohort study of 1,037 New Zealanders born in 1972/3. Research psychiatric diagnoses had been made at ages 11, 13, 15, 18, 21, 26, 32 and 38 years, with an overall participant retention rate of 96%. The structured diagnostic interview instruments used for the diagnoses were the Diagnostic Interview Schedule (DIS) for adult ages and the Diagnostic Interview Schedule for Children (DISC) for both parent (DISC-P) and child/youth (DISC-C) informants at ages 11 to 15-years-old. No bipolar disorder diagnoses were made until age 21, when 19 cases of 'manic episode' emerged (Newman et al. 1996). This age of onset would be consistent with the classical view of bipolar disorder.

By age 26, 48.2% of the cohort met criteria for a 1-year prevalence of a DSM-IV diagnosis. There had been 29 cases of mania including three cases who did not meet research criteria but who had been treated by their own doctors for this diagnosis. Otherwise, diagnoses were based on the DISC-C if corroborated by parent-report and severity measures. This equated to a 12-month prevalence of 3%. It is not clear if this includes hypomania as well as mania. This was an increase from 2% for a diagnosis of 'manic episode' for the cohort at age 21 (Newman et al. 1996) and zero cases at age 18 (Feehan et al. 1994) and age 15 and 11 (McGee R et al. 1990). Therefore, the paediatric prevalence from the Dunedin birth cohort study was 0%, but young adult cases manifested later.

Interestingly, prior diagnoses in those with Bipolar-I at age 26 included CD, ODD and juvenile depression. Moreover, those adults with mania histories were less likely than adults without mania to have had a childhood ADHD diagnosis, which is the opposite of the pattern of very high comorbidity with ADHD inherent in the PBD hypothesis.

Kim-Cohen et al. (2003) stated: 'Diagnoses of manic episode and schizophrenia were not obtained at juvenile ages' (p. 710). This is clearly contrary to the conclusion of Van Meter et al., who claimed a 1.8% prevalence as interpreted from this study (Figure 6.2).

6.5.1.2 **Verhulst et al. 1997 (conducted 1993, the Netherlands).**

The Dutch study (Verhulst et al. 1997) did not assess PBD among pre-pubertal children. It included seven hundred and eighty 13–18-years-old adolescents, using both parent (DISC-P) and the adolescent (DISC-C) to arrive at 6-month prevalence rates for DSM-III-R diagnoses. Van Meter, Moreira and Youngstrom (2011) quote the highest figure reached in the study's methodology: that of 2.8% having Bipolar-I or II disorder (Figure 6.2).

However, the Dutch study actually indicated a rate of 0% if parent and adolescent responses were correlated for agreement rather than summated (Figure 6.2). On parent interview, 21.8% of adolescents had any psychiatric disorder, 1.1% had mania, and nil had hypomania; on the basis of the adolescent interview, 21.5% had any disorder, 0.9% mania and 0.9% hypomania. Unfortunately, there was little cross-informant agreement. If both interviews were summated for diagnosis, then 35.5% of the adolescents had a 6-month prevalence of psychiatric disorder, 1.9% had mania and 0.9% had hypomania (i.e. 2.8% combined). However, if only the parent and adolescent interviews that concurred were used, then the rates slump to just 4% having any psychiatric disorder and zero cases of mania or hypomania. Further undermining Van Meter et al.'s conclusions, Verhulst et al. discussed these aspects, pointing out that:

> although the prevalence rates based on the DISC-P and DISC-C separately were nearly identical (21.8% and 21.5%), each instrument identified different subjects in most cases. (p. 335)

In concert with the view that community surveys overestimate psychopathology with false positives, Verhulst et al. (1997) noted that very few of the adolescents were functionally impaired apart from: 'those subjects who met criteria for a DISC-P *and* a DISC-C diagnosis [who] showed the most impairment.' (p. 335; italics added).

6.5.1.3 **Canals et al. 1997 (conducted 1994, Spain).**

The Spanish study (Canals et al. 1997) also did not include pre-pubertal children. It used the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), to interview two hundred ninety 17 – 18-year-old adolescents for point prevalence of psychiatric disorders. They found using ICD-10 criteria that 29.3% had a current psychiatric disorder. Of these, 2.4% displayed hypomania according to ICD-10 criteria, but 0% when DSM-IIIR criteria were used, and nil cases of mania by either set of criteria. Van Meter, Moreira and Youngstrom (2011) chose to use the ICD figure from Canals et al. (1997) (Figure 6.2) whereas all the other 11 studies used DSM criteria. Nearly all the hypomania cases in Canals et al. (1997) were female, and the authors commented that they might have been false positives or cases of cyclothymia. This was very much a study of older adolescents, and it is questionable why the term 'PBD' was applied.

6.5.1.4 **Lynch et al. 2006 (conducted 2002, Republic of Ireland).**

The Irish study (Lynch et al. 2006) surveyed seven hundred twenty-three 12 – 15-year-old youth in urban Dublin schools and found no cases of bipolar disorder (Figure 6.2). Subjects and their parents were interviewed with the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for lifetime prevalence of psychiatric disorder. The methodology was refined:

> [I]nterviews with parents and child are combined and where there is disagreement ... the interviewer makes a clinical decision regarding diagnosis or not. (Lynch et al. 2006, p. 560)

The study found lifetime rates of 19.9% for any psychiatric disorder, 8.4% for affective disorder (depression or dysthymia), 4.3% for anxiety disorder, 3.7% for ADHD, 1.2% for CD and 2.3% for ODD. Whilst the authors noted these rates were comparable with international epidemiological studies, their study had only 51% of eligible students enrol due to absenteeism and non-completion of consent forms. Therefore, it is possible that the survey did not detect any cases of bipolar disorder because such cases may have been amongst the absentees. Nonetheless, the prevalence amongst participants was 0%.

6.5.1.5 **Benjet et al. 2009 (conducted 2005, Mexico).**

The Mexican study (Benjet et al. 2009) also included children as young as 12. They interviewed three thousand five 12–17-years-old youth using the World Mental Health Composite International Diagnostic Interview (CIDI) in Mexico City. Parents were not interviewed. They found a 12-month prevalence of any psychiatric disorders of 39.4%: anxiety disorders 29.8%; mood disorders 7.2% which included 2.5% 'bipolar disorder (broad)' that they had defined as 'bipolar-I and bipolar-II disorders combined'; impulse and disruptive behaviour disorders 15.3%; and substance use disorders 3.3%. The authors did not discuss bipolar disorder in the text, however they indicated that adolescents completing the CIDI would be considered to have a 'serious' disorder if their responses indicated Bipolar-I disorder. From the article's table, this equated to 82% of the 2.5%, thus 2.05% had Bipolar-I and 0.45% Bipolar-II (see Figure 6.2). They acknowledged the high rate of overall psychiatric disturbance and postulated that rapid globalisation, urbanisation and other psychosocial stressors in Mexico City could be contributory. The high rates reported amongst an adolescent sample, with no corroboratory alternative informant source, and the lack of impairment criteria, cast doubt on the validity of these findings.

6.5.1.6 **Stringaris, Santosh et al. 2010 (conducted 2007, United Kingdom).**

The UK study (Stringaris, Santosh et al. 2010) was a follow-up study of the British Child and Adolescent Mental Health Survey (B-CAMHS04). It involved a sample of five thousand three hundred twenty-six 8 – 19-year-olds. Both parents and youth (those at least aged 11-years-old) were interviewed with the Development and Well-Being Assessment (DAWBA) and Strengths and Difficulties Questionnaire (SDQ). A co-author was Leibenluft, director of the child and adolescent mood disorders unit at the US NIMH. Due to the controversy over early-onset bipolar disorder that was starting to arise in the United Kingdom by that time, this survey attempted to vigorously apply DSM-IV criteria.

The main study findings regarding DSM-IV manic or hypomanic episodes were as follows: a lifetime prevalence of Bipolar-I disorder plus Bipolar-II disorder of 'between 0.1% and 0.3% in 16 – 19-year-olds' and only a single case (0.028%) for 8 – 15-year-olds, which is far lower than the 1.2% quoted by the Van Meter et al. Stringaris, Santosh et al. quoted the overall rate for Bipolar-I and Bipolar-II as a lifetime prevalence of 0.1% (Figure 6.2).

However, with regard to subthreshold Bipolar-NOS cases where manic symptoms lasted between (a few) hours and 3 days, there was in effect a 10-fold increase in comparison to Bipolar-I and Bipolar-II: 1.1% by parent report and 1.5% by youth report. There were significant comorbid disruptive behaviour disorders reported with the parent-report group and disruptive behaviour disorders and anxiety disorders by the self-report group. Reflecting the findings in the Dutch study, the individuals identified were not the same for the two groups: the correlation between parent and youth report was no better than chance and the κ value was only 0.02. The authors were cautious as to whether Bipolar-NOS was therefore on the same spectrum as full DSM-IV Bipolar-I disorder and called for further research that avoided the semantic problem of using the bipolar label for subthreshold cases in favour of more neutral terms like mood lability.

Despite these comments from the authors that suggested a rate of 0.1% for Bipolar-I and Bipolar-II disorder, Van Meter, Moreira and Youngstrom (2011) reported an overall lifetime prevalence of bipolar spectrum disorders from this study as 1.2%. It is unclear if this is the weighted prevalence figure they derived in their statistical meta-analysis or it could be the Bipolar-I and Bipolar-II group plus the parent-reported Bipolar-NOS group (Figure 6.2).

6.5.2 The six US studies

6.5.2.1 **Kashani et al. 1987 (conducted 1986).**

Kashani et al. (1987) was the first US community-based epidemiological study of lifetime prevalence of psychiatric disorders in adolescents. It was conducted in the US Mid-West. The study examined 150 adolescents (75 males, 75 females) aged 14–16-years-old, interviewed on home visits with the Diagnostic Interview for Children and Adolescents–Child Version (DICA-C), and interviewed parents with the DICA–Parent Version (DICA-P) as well as having parents complete the Child Behaviour Checklist amongst a range of other questionnaires. Despite information from the DICA-P being available, Kashani et al. (1987) reported that 'the final diagnosis was based on the (DICA-C) (p. 585). The authors justified their decision by suggesting that child reports increase in reliability with age, while parent reports become less reliable. Diagnosis also required agreement by both a psychologist and child psychiatrist independently reviewing the questionnaires and considering impairment criteria.

Although 62 adolescents (41.3%) were deemed to have a DSM-III disorder based on the DICA-C, when criteria for impaired functioning were included the total prevalence of a psychiatric disorder was 18.7% (28 adolescents). Only one adolescent girl (0.7% of the total sample) was considered to have mania in Kashani et al. (1987) as corroborated by her parent (Figure 6.2). In the review of the data (Carlson & Kashani 1988) adolescent reports of manic symptoms were frequent at 13.3% but none met impairment criteria, including presumably for the previous case of mania. Three adolescents (2%) had a major depression as well as manic symptoms and may have had cyclothymia (Carlson & Kashani 1988). Hence the true rate of Bipolar-I and Bipolar-II disorder in this study was 0%.

6.5.2.2 **Lewinsohn et al. 1995 (conducted 1988).**

Lewinsohn, Klein, and Seeley (1995) reported on the Oregon Adolescent Depression Project (OADP). In their survey of 1709 adolescents aged 14–17 years old, repeated with 1507 at one-year follow-up, they found two cases of Bipolar-I for a 0.1% lifetime prevalence, 11 cases of Bipolar-II (0.6%), and five cases of cyclothymia (0.3%; Figure 6.2). In addition, Lewinsohn, Klein and Seeley (1995) had used a broad measure for diagnosing 97 teens with Bipolar-NOS (5.7%) who were "subjects who reported experiencing an abnormally and persistently elevated, expansive or irritable mood, but never met criteria for bipolar disorder" (p. 454) Parents were not interviewed. Van Meter et al. (2011) commented on this study by saying:

> It remains for clinical validation studies and longitudinal follow-up to determine whether persons meeting these broader definitions have a similar aetiology and course to those with presentations satisfying more narrow criteria. (p. 1254)

This statement made in 2011 is somewhat misleading, given that in 2000, five years after Lewinshohn et al.'s original study, he and his colleagues reassessed a large proportion (81%) of the original cohort around the time of their 24th birthdays. The combined lifetime rate of Bipolar-I disorder (n = 8), Bipolar-II disorder (n = 13) and cyclothymia (n = 2) was 2.1%. Strikingly, none of the 5.7% of original adolescents (n = 97, of whom 49 were in the follow-up at age 24) with Bipolar-NOS symptoms had gone on to exhibit bipolar disorder, although many developed major depressive episodes and impaired social functioning (Lewinsohn, Klein & Seeley, 2000). Six new cases of Bipolar-I or -II disorder arose between ages 19–24, but none of these had Bipolar-NOS on the first assessment. The authors noted a very low rate (1%) of

'switching' from major depressive disorder to bipolar disorder in this community sample. The true rate of mania, then, in the 1995 study of Lewinsohn et al. is 0.1% and of bipolar spectrum disorders, 0.9%.

6.5.2.3 **Costello et al. 1996 (conducted 1994).**

As reported by Van Meter, Moreira and Youngstrom (2011), the Great Smoky Mountains study of one thousand fifteen 9 – 13-year-old children (Costello et al. 1996), found a 3-month prevalence rate of 0.1% of hypomania and nil cases of mania. A rate of 20.25% for any psychiatric disorder was also found. Both subjects and parents were interviewed using the Child and Adolescent Psychiatric Assessment questionnaire (CAPA) and "diagnosis was made on basis of 'combined reports' where a symptom is regarded as being present if either the parent or the child reports it" (p. 1131). A follow-up of this study (Costello et al. 2003) did not mention mania or bipolar disorder in their statistics, though the total 3-month prevalence for any psychiatric disorder was 13.3% and disorders were categorised under disruptive behaviour, depressive disorder, anxiety disorder and substance use disorder categories.

6.5.2.4 **Andrade et al. 2006 (conducted 1994).**

Andrade et al. (2006) did not assess any preteen children; this was a Hawaiian study of 619 adolescents aged 13–21-years-old using the DISC-C. Parents were not interviewed. This study found a lifetime prevalence of psychiatric disorder of 26.0% and of 'mania-hypomania' of 1.4% (Figure 6.2). There was no elaboration on the subject of mania/bipolar disorder in the article. Van Meter, Moreira and Youngstrom (2011) reported the figure as 1.5% (Figure 6.2), presumably due to the effects of loading in the statistical meta-analysis.

6.5.2.5 **Gould et al. 1998 (conducted 1996).**

Gould et al. (1998) surveyed 1,285 children and adolescents aged 9–17-years-old, interviewing the subjects (DISC-C) and their parents (DISC-P) in the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) study. The focus of the article was suicidality, but rates of DSM-III-R psychiatric disorders were given. The 6-month prevalence of any psychiatric disorder was 30.4%, the prevalence of mania was 1.2% based on summation of parent and adolescent reports (Figure 6.2). This is calculated from results detailed in table 2 in Gould et al. (1998) where the number of youth with 'mania' was

recorded as 16 out of a cohort of 1285. Van Meter, Moreira and Youngstrom (2011) quoted it as 1.3% (Figure 6.2). The text of Gould et al. (1998) reported diagnoses of 'hypomania' as well as 'mania' made, but only 'mania' was listed in the results table, so either no cases of hypomania were found or both mania and hypomania were listed as 'mania' in the table.

Gould et al. (1998) report in their abstract and methodology sections that the age range of subjects was "9 to 17 years", though "12 youths (0.9%) had turned 18-years-old by time of interview". But in a table they list two age ranges of "7–12 years" and "13–18 years". Van Meter, Moreira and Youngstrom (2011) thus cite the age range as "7–18 years".

6.5.2.6 **Kessler et al. 2009 (conducted 2003).**

Kessler et al. (2009) also did not assess any preteen children; they reported on structured interviews with a representative sample of three hundred forty-seven 13 – 17-year-old adolescents from the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). The 329 were representative of the full NCS-A sample of 10,148. This study used the Composite International Diagnostic Interview (CIDI) for telephone screening and both the CIDI and the K-SADS for later face-to-face interview with both the adolescent and parent. The timing of this study coincided with growing popularity of the PBD diagnosis and the authors were keen to ascertain rates for bipolar spectrum disorder (BPSD), dedicating a section of their article to discussing this. They defined BPSD as Bipolar-I, Bipolar-II or subthreshold bipolar disorder and found, based on the K-SADS, an overall adolescent lifetime prevalence of any DSM-IV psychiatric disorder of 52.5% and 6.2% for BPSD but that rates of Bipolar-I were much lower, however, at 1%, Bipolar-II 1.3% and subthreshold bipolar at 3.9%. The CIDI rate of Bipolar-I disorder was 0.5%. The CIDI rate of BPSD was even higher at 6.7% with rates of Bipolar-I at 0.5% and Bipolar-II at 1.8% (Figure 6.2). The authors acknowledged that they chose not to use the severity ratings in the CIDI and if they had that would have decreased the prevalence rates.

6.6 Discussion

6.6.1 Marked discrepancies between international and US surveys

The meta-analysis by Van Meter et al., of which the 12 contributing studies assessed mostly adolescents, contends that the overall rate of occurrence of bipolar spectrum disorder, not

just mania, is about 1.8% and further, that it is the same worldwide. However, a re-examination of the studies that comprise the meta-analysis revealed that rates of Bipolar-I in the US were in fact quite low (0.0% – 1.0%) with understandably higher rates for bipolar spectrum disorder (up to 6.7%) depending on how it is defined.

Outside the US, rates were perhaps even lower (0.0% – 0.1% for 16 – 19-years; or 0.0% – 0.04% for 8 – 19-years in the UK study), except in Mexico (Benjet et al. 2009: 2.05%) for mania. In particular, the careful UK study (Stringaris, Santosh et al. 2010) found the lifetime prevalence of Bipolar-I and Bipolar-II disorder to be very low in childhood and early adolescence (0.028% for 8 – 15-year-olds).

Inconsistencies between studies are partly accounted for by methodological differences, especially differences in the nature and number of informant reports used: combination of parent and adolescent reports generally results in higher accuracy.

There are also markedly divergent views amongst researchers and clinicians on what constitutes bipolar disorder in the paediatric age group. This is an issue for the adult population as well. These views, sometimes described as 'liberal' and 'conservative' perspectives, add substantial confusion to the field (Carlson & Klein 2014). Bipolar disorder, outside of florid euphoric manic episodes fulfilling DSM-5 duration criteria, can be considered to be very much in the eye of the beholder. This was highlighted in the transatlantic comparison study of child psychiatrists' diagnosing practices in five written clinical vignettes. (Dubicka et al. 2008).

6.6.2 Age ranges not truly indicative of 'paediatric' categorisation

The vast majority of the 16,222 subjects in the 12 epidemiological studies were adolescents. Some were young adults (four studies included 18-year-olds, one study included 19-year-olds, and one study included 21-year-olds). Only four of the 12 studies included children under age 12 (from ages 8, 9 and 11), but these four studies also included adolescents. This age group is not representative of the preteen PBD cohorts in the US studies that launched the PBD phenotypes. All of Wozniak et al.'s original cohort of 43 children were under age 12 (Wozniak, Biederman, Kiely, et al. 1995). Geller et al. (1995)'s original cohort of 26 children and teens

included nine under age 13 (mean age of PBD onset 4.0 ±2.9-years), while the remaining 17 were aged between 13 and 18-years (mean age onset 10.9 ±2.9-years).

In contrast, the young people in the dozen community epidemiological surveys in the meta-analysis of Van Meter, Moreira and Youngstrom (2011) were significantly older than these PBD research cohorts. There was no clear evidence of any preteen cases diagnosed. They are in general older than the large number of children diagnosed with bipolar disorder in preadolescent US psychiatric inpatient units (Blader & Carlson 2007).

6.7 **Conclusion**

The meta-analysis of 12 community epidemiological surveys of mainly adolescent youth conducted by Van Meter and colleagues used a dozen studies of interest. However, the heterogeneous nature of these 12 studies lessens their combined suitability for a statistical meta-analysis. In terms of individual studies, the actual rates of PBD were generally substantially lower than the 1.8%, claimed, particularly in non-US surveys. If both parent and adolescent reports were required to meet the diagnostic threshold, prevalence rates in fact fell to close to zero. The narrative re-examination of the original studies suggests that bipolar disorder is extremely rare before the generally accepted age of onset in later adolescence.

Furthermore, the 12 studies do not support the conclusions of the authors: that "the prevalence of paediatric bipolar disorder is similar to current prevalence estimates of bipolar disorder in adults," nor that "the prevalence of paediatric bipolar disorder is not different in the United States, relative to other countries." Rather, the 12 studies suggest that where best-practice methodology was used, and parent and child reports correlated for agreement, and impairment criteria was included, that rates of Bipolar-I disorder in children and adolescents were close to zero outside the US and only slightly higher in the US, though rates of bipolar spectrum disorder were slightly higher. Authors who have cited the meta-analysis need to critically examine the original studies.

6.8 **Critique of updated meta-analysis by Van Meter et al. (2019b)**

As presented in Chapter 4.8.8.3, Van Meter, Moreira and Youngstrom (2019b) added eight new epidemiological studies to the original 12 from which they subtracted the NZ study of

Kim-Cohen et al. (2003), for a total of 19 studies which by meta-analytical methods they derived a doubling of the PBD 'bipolar spectrum' prevalence rate to 3.9%, while the Bipolar-I rate halved to 0.6%.

6.8.1 **Comparison of prevalence rates in the 8 studies**

The eight new surveys covered by the Van Meter, Moreira and Youngstrom (2019b) are illustrated in Figure 6.3 and examined in the same manner as the first twelve.

Source Subjects	Location Year completed Criteria	Instrument Prevalence period Age	Informant Critique	Van Meter et al. (2019b)			BD-I %	Total Bipolar Spectrum %	
				BD-I	Undiff. BD BD-II	Bipolar Spectrum			
Päären et al, 2014 N = 2,300	Sweden 1991-1993 DSM-III-R	BDI-C CES-DC Attempted Suicide DICA-R-A Lifetime 16-17 years	Youth report only Methodology does not allow for accurate community prevalence. Two stage screening with depression questionnaires followed by a diagnostic interview for hypomania	0.04%	-	4.0%	1/2,300 = 0.04% fulfilled criteria for a manic episode	62/2,300 = 2.7%	
Tijssen et al, 2010b N = 1,395 or 705	Germany 1994 Follow-up 1996, 2002 DSM-IV	DIA-X/M-CIDI Lifetime 14-17 years	Youth report only. 37 cases in 1,395 identified as at least 4 days hypomanic/manic lifetime symptoms, but these excluded from follow-up cohort of 705, as study focused on development of new symptoms	-	2.7%	14.3%	Not defined	37/1,395 = 2.65%	
Roberts et al, 2007 N = 4,175	Texas, USA 2000 DSM-IV	DISC-IV 12 mth 11-17 years	Youth report only for diagnosis Divided results according to whether impairment criteria of DISC-IV or CGAS were applied or not.	0.4%	1.2%	-	0.39% (with/out impairment) 0.31% (DISC impairment) 0.22% (CGAS impairment)	1.2% (with/out impairment) 0.31% (DISC impairment) 0.31% (CGAS impairment)	
Kozloff et al, 2010 N = 5,673	Canada 2002 DSM-IV	CIDI Lifetime 15-24 years	Youth report only. Diagnoses on DSM-IV criteria but more liberal duration criteria of "several days or longer".	2.0%	-	-	Not defined	All ages 15-24 years 15-18 years 19-24 years	3.0% 2.1% 3.8%
Anselmi et al, 2010 N = 4,452	Brazil 2005/2006 DSM-IV/ICD-10	DAWBA [Estimated prevalence reads as based on cases in the diagnostic phase. Formula in the stats section] 11-12 years	Child plus mother informants combined with psychiatrist adjudication where discrepant	0%	-	-	0%	0%	
Pan et al, 2014 N = original sample = 9,937; final sample = 1,554 high-risk + 958 random-selection = 2,512	Brazil 2009 screening 2010-2011 DSM-IV	DAWBA Lifetime 6-12 years Parents of 9,937 6- to 12-year-old children were interviewed using the Family History Survey. A sample of 2,512 random + high-risk children were selected for parent interview using the DAWBA	Parent/caregiver only informant 'Exuberant' hypomanic symptoms not associated with impairment or psychopathology 'Under-control' hypomanic symptoms overlap with ADHD and ODD/ CD	-	0.2%	1.8%	0.2% (BD-I/BD-II) 0.2%* (* weighted prevalence – pers. comm. Pan-Parry, 2019)	1.8% 1.4%* (* weighted prevalence – pers. comm. Pan-Parry, 2019)	
Vizard et al. (2018) N = 9,117	England 2017 ICD-10	DAWBA Lifetime 2-19 years	2-4-year-old (parent) 5-10-year-old (parent + teacher) 11-16-year-old (parent + youth + teacher) 17-19-year-old (parent + youth)	0.1%	-	-	Not defined ICD-10 F-30/F-31 codes include mania/hypomania/BD-I/BD-II/BD-undifferentiated	0.0% 5-16-year-olds 0.1% 17-19-year-olds NB by age/gender the two groups with cases were 11-16-year-old boys (0.1%) and 17-19-year-old girls (0.3%) Pers. comm. Ford-Parry, 2019 indicated youngest case bipolar spectrum disorder was 16-years-old.	
Karacetin et al. (2018) N = 5,842	Turkey	K-SADS-PL Lifetime 2014-2015 Turkish school year 7-10 years	Parent only	0%	0%	0%	0%	0%	

Figure 6.3: The eight additional epidemiological studies meta-analysed by Van Meter, Moreira & Youngstrom (2019b)

6.8.2 Narrative analysis of the eight newer surveys

6.8.2.1 Päären et al. 2014 (conducted 1991-1993, follow-up 2006-2008, Sweden).

This Swedish study screened 2,300 of all 2,465 adolescents age 16 – 17-years-old in the town of Uppsala during 1991-1993 for a lifetime history of depression. Screening utilised the Beck Depression Inventory-Child (BDI-C) and Centre for Epidemiological Studies – Depression Scale for Children (CES-DC). Three hundred and fifty-five (77% female) screened positive and three hundred and fourteen then participated in the screening with the Diagnostic Interview for Children and Adolescents (revised for DSM-III-R, adolescent version, DICA-R-A) for hypomanic symptoms ("hypomania spectrum"). Additionally, 317 of 355 controls who had not screened positive for depression were also assessed with the DICA-R-A.

'Hypomania spectrum' was defined as: full-syndromal hypomania for at least 4 days duration, brief-episode hypomania with full symptom criteria but <4 days, or subsyndromal hypomania (1 or 2 main symptoms – elevated mood, grandiosity – with 1 or 2 additional symptoms for total of at least 3 symptoms, duration unspecified but most were >4days).

The findings from the DICA-R-A interview, from both the combined positive and negatively screened cohort of 631 adolescents, were:

> 90 participants with hypomania spectrum (40 full-syndromal, 18 with brief episode, and 32 subsyndromal), 197 participants with major depressive disorder (MDD) and 229 controls. (p. 4)

There was high comorbidity: 78% of hypomania spectrum, 80% of MDD and 25% of controls reported at least one lifetime axis I disorder.

Fifteen years later, in 2006-2008 at ages 31 – 33-years-old, the cohort was diagnostically reviewed with the Mini International Neuropsychiatric Interview Plus (MINI Plus) as well as instruments to screen for personality disorders. The participant rate at follow-up was 71% for hypomania spectrum (n = 64), 66% for MDD (n = 130) and 65% (n = 148) for control groups. Examination of Swedish national registers allowed for tracking hospitalisations, psychiatric outpatient care and medication prescriptions to augment data.

The 15-year follow-up findings reported by Päären et al. (2014) focussed on: (1) comorbidity with non-mood axis-I DSM-IV disorders (mainly anxiety disorders), which were found with 56% of the full-syndromal hypomania group, 53% of all the hypomania spectrum group inclusive of full-syndromal hypomania, 57% of the MDD group and 28% of the controls; comorbidity with DSM-IV personality disorders, which were found with 35% of the full-syndromal hypomania group, 29% of the hypomania spectrum group, 20% of the MDD and 8% of the control groups.

The authors also noted that:

> [C]ontinued mood disorder in adulthood (MDD, bipolar disorder, or dysthymia) was reported by 60.9% of the hypomania spectrum group and 70.0% of the MDD group. (p. 9)

However, only 24% of hypomania spectrum, 21% of MDD and 7% of controls had been treated for a diagnosed mental disorder. Nonetheless 31% of hypomania spectrum, 28% of MDD and 13% of controls had taken antidepressants, but just 7% of hypomania spectrum (n = 4) and 2% of MDD and no controls had been prescribed antipsychotics. None of the hypomania spectrum and just 2% of MDD had been prescribed anticonvulsants and none had been prescribed lithium.

In a separate article (Päären et al. 2013) reported that of the 64/90 adolescents at follow-up at age 31-33, who had reported lifetime hypomanic syndromes at baseline in 1991-1993, 38 adults (59%) reported an adult MDD, only four (6%) reported recurrence of hypomania and only two (3%) reported a manic episode. This is a very low rate of conversion of adolescent hypomania syndromes into adult bipolar disorder. The authors stated it was unlikely that the 29% of the hypomania spectrum adolescents lost to follow-up had converted to adult bipolar disorder as the register data showed “only a few received inpatient or outpatient care for mental disorders” (Päären et al. 2014, p. 12). The authors concluded that “these results … cast doubt on the diagnostic usefulness of a broader spectrum of hypomania in adolescence” (p. 12).

6.8.2.2 **Tijssen et al. 2010b (conducted 1994-2002: 8-year follow-up, Germany).**

This German study (was conducted on one thousand three hundred ninety-five 14 – 17-year-old adolescents in the Munich region, who were enrolees in a larger study (the Early Developmental Stages of Psychopathology [EDSP] study). The participants were interviewed with a computerised and German version of the World Health Organisation's Composite International Diagnostic Interview (DIA-X/M-CIDI) to derive lifetime DSM-IV diagnoses as well as syndromes and subsyndromal mental symptoms. Minimum duration criterion was set at two weeks for assessing depressive symptoms and 4 days for hypomanic/manic symptoms.

The participants were interviewed in 1994 and then three further times over an 8-year period. The retention rate was 88% at 18 months, 83% at 3.4 years and 73% at 8.3 years. At the first follow-up interview, a parent was also interviewed primarily to collect family psychiatric history and whether the adolescent had ever been diagnosed with ADHD, otherwise it appears the interviews were conducted with the adolescent participants.

The main aim of this study was to examine risk factors that may presage mood symptoms and episodes. In particular: the presence of family psychiatric history, negative life events, substance use, ADHD diagnosis and personality factors. The last was assessed using the Tridimensional Personality Questionnaire (TPQ) developed by Cloninger (1987).

Because the study focused on risk factors related to the appearance of "subthreshold expression of bipolar psychopathology", all 37 (2.65%) of cases of hypomanic/manic episodes were excluded at the baseline interview (p. 255). Additionally, any participants (n = 653) on whom there was less than full data from all four interviews were excluded, leaving a study cohort of 705 participants. The authors reported that of these 705 participants, 162 (23.0%) had a lifetime history of subsyndromal hypomanic/manic symptoms at baseline and 125 (17.7%) had had subsyndromal depressive symptoms. They then examined the 705-162 (= 543) who had never had any hypomanic/manic symptoms at baseline, and the 705-125 (= 580) who had never had any depressive symptoms at baseline in the three follow-up interviews for onset of new hypomanic/manic symptoms or depressive symptoms and then persistence of such symptoms and relationship to the risk factors.

With regards to bipolarity, they found correlations between cannabis use and novelty-seeking temperament with the onset of hypomanic/manic symptoms. However, no risk factors had statistically significant positive correlations for persistence of hypomanic/manic symptoms at later follow-up. Surprisingly there was a strong negative correlation for novelty seeking temperament in adolescence with persistence of hypomanic/manic symptoms into adulthood.

However, perhaps the most likely subjects to develop hypomania/mania had been excluded. The authors noted a limitation in their study was:

> [T]he exclusion of individuals with manic and depressive symptoms at baseline, necessary to ensure that associations between risk factors and follow-up symptoms were truly predictive, resulted in a decrease in statistical power. (p. 263)

They postulated that the transitory nature of subsyndromal hypomanic/manic symptoms and the link with novelty seeking temperament in adolescence that faded by young adulthood represented physiological dopaminergic mechanisms of adolescent development. Tijssen et al. (2010b) concluded:

> This hypothesis would fit well with the observed high prevalence of manic symptoms reported in adolescents that are transitory for the great majority of individuals. (p. 263)

It appears from Tijssen et al. (2010b)'s article that none of the 705 participants developed a full hypomanic/manic episode over the 8-year follow-up. As there was no follow-up data on the 37 (2.65%) of the original 1,395 at baseline who recorded a lifetime hypomanic/manic episode of >4 days duration, it is unclear how many of this group might have had recurrent episodes measurable in the study's 8-year follow-up period, which could have been a means of validating true bipolar disorder in this group.

6.8.2.3 **Roberts RE, Roberts & Xing 2007 (conducted 2000, USA).**

This study utilised data from the Teen Health 2000 (TH2K) study that surveyed a representative sample of 4,175 youths aged 11-17-years-old and one of their caregivers from a metropolitan area of Texas (Roberts RE, Roberts & Xing 2007). The DISC-IV was used to examine for 12-month prevalence of DSM-IV diagnoses. Impairment was measured using the

DISC-IV impairment scale and the Child Global Assessment Scale (CGAS). The authors seem to have used youth reports for making of DSM-IV diagnoses, adding caregiver reports to possibly ascertain level of impairment and demographic data for analysis of risk and protective factors. They state: “we did not interview parents about the DSM-IV disorders assessed by youth interview”, noting that “many studies have demonstrated considerable discordance in parent-child reports of psychopathology” and “there is little consensus on how parent and youth reports should be combined in epidemiologic studies” (p. 7).

The findings were divided according to DISC-IV without impairment, with DISC-IV impairment criteria, or with CGAS impairment criteria. They found a 12-month prevalence of all DSM-IV disorders of 17.1% (no impairment), 11.1% (DISC-IV impairment) and 5.3% (CGAS impairment).

The respective findings for mania were 0.39% (95% C.I. 0.18-0.61), 0.31% (0.12-0.51), 0.22% (0.05-0.39) and for hypomania were 0.81% (0.50-1.12), 0%, 0.09% (0-0.20). By comparison the findings for MDD were 1.7%, 1.5%, 0.7%; dysthymia 0.3%, 0.3%, 0.2%; ADHD 2.1%, 1.9%, 0.85%; CD/ODD 6.5%, 3.6%, 1.8%; any anxiety disorder 6.9%, 3.4%, 1.4%; SUD 5.3%, 2.7%, 2.4%. The youngest (11 and 12-year-olds) had roughly half the odds ratios of having a mood disorder than both the 13 – 15-year-old and 16 – 17-year-old cohorts, but hypomania/mania were not distinguished from MDD/Dysthymia.

6.8.2.4 **Kozloff et al. 2010 (conducted 2002, Canada).**

This study extracted data from the representative Canadian Community Health Survey: Mental Health and Well-being (CCHS 1.2) survey conducted in 2002 of 36,984 people aged 15-years and older. The CCHS 1.2 used structured interviews (86% face to face, 14% by phone) with the subjects using the World Mental Health-Composite International Diagnostic Interview (WMH-CIDI) based on DSM-IV criteria. Caregivers were not interviewed. Kozloff et al. looked at the data from the 5,673 participants aged 15 – 18-years-old and 19 – 24-years-old.

The CCHS 1.2 used DSM-IV criteria for diagnosis of a lifetime manic episode but rather than the full 7-day duration criteria, defined a manic episode of lasting “several days of longer” (p. 351). Kozloff et al. presumed that:

> [T]he sample likely included subjects with BD-I as well as BD-II and 'not otherwise specified' but the CCHS 1.2 interview did not include criteria required to accurately differentiate these subgroups of BD. (p. 351)

Kozloff et al. found the:

> [O]verall weighted lifetime prevalence rate of BD among 15-24-year-olds was 3.0% (95% C.I. 2.5-3.6): 2.1% (1.4-2.7) among adolescents 15-18-years and 3.8% (3.0-4.6) among young adults aged 19-24. (p. 352)

There were high lifetime comorbid anxiety disorders (46.6%) and 12-month problematic substance use prevalence (50.4%).

In their discussion the authors noted these rates of bipolar disorder meant that "BD in youth is a fairly common, highly comorbid disorder" (p. 353). They note the rates were higher than in older adults and cited similar research findings that the highest lifetime rates of Bipolar-I disorder were among 12 – 29-year-olds (Grant et al. 2005) and Bipolar-I disorder and Bipolar-II disorder among 18 – 29-year-olds (Kessler et al. 2005). They postulated that attrition from suicide and misadventure may lead to the decreasing rates of bipolar disorder in older adults, but also listed several limitations of their study that may have over-estimated the bipolar disorder rate in this youth and young adult sample: 1) the CCHS 1.2 survey used a more liberal duration criteria than strict DSM-IV; 2) the WMH-CIDI was not calibrated for adolescents and "may not accurately distinguish BD from other disorders [such as] ADHD and conduct disorder [which are] more common in adolescents" (p. 353); 3) episodes may be difficult to distinguish from "extreme and frequent mood swings" that "adolescents tend to experience more than adults" (p. 353); 4) "the CCHS 1.2 survey relied on self-report without the support of collateral information" (p. 353).

6.8.2.5 **Anselmi et al. 2010 (conducted 2005-2006, Brazil).**

This Brazilian study involved children from the town of Pelotas in southern Brazil where all births in 1993 were enrolled into the Brazilian Birth Cohort Study. Anselmi et al. screened 4,452 preadolescents (mean age 11.3-years-old) and their mothers with the Strengths and Difficulties Questionnaire (SDQ) in 2004/2005 and later conducted a diagnostic phase of interviews with the preadolescent children (mean age 12.4-years-old) and their mothers using

the Development and Well-Being Assessment of Children and Adolescents (DAWBA) in 2005/2006. Prevalence rates were calculated based upon present symptomatology:

> [A]ccording to the formula ... Pe = cd + nns(1 – npv)/*n* ... where Pe is the estimated prevalence, cd is the cases during the diagnostic phase, nns is the number of negative screenings that were not assessed in the diagnostic phase, npv is the negative predictive value of SDQ and *n* is the sample size. (p. 138)

From the SDQ screening phase, all who had screened positive above an *a-priori* severity of SDQ symptoms cut-off (*n* = 122), and a random selection of those who were below the cut-off (*n* = 158) for a total of 280 children and their mothers, were interviewed using the DAWBA. Diagnoses were based on both parent and child report with adjudication of final diagnosis by one of the child psychiatrist authors where parent and child interviews were discordant.

Anselmi et al. calculated by this methodology that "479 preadolescents out of the 4,448 participants of the 1993 birth cohort would present at least one psychiatric disorder according to either the ICD-10 or DSM-IV" (p. 138). They listed all diagnoses in a table. The main findings were: any DSM-IV diagnosis 10.8% (95% C.I. 7.1-14.5) and the rates were identical for any ICD-10 diagnosis; any anxiety disorder 6.0% DSM-IV and 6.2% ICD-10; any depressive disorder 1.6% (0.4-3.6) DSM-IV and same for ICD-10; any ADHD/hyperkinetic disorder 4.1% (1.6-6.4) DSM-IV and 2.7% (0.9-5.0) ICD-10; any oppositional-conduct disorder 4.4% (1.6-6.4) rates identical for DSM-IV and ICD-10; eating disorders 0.1% (0.3-0.5) rates again equal for DSM-IV and ICD-10; tic disorders 1.3% (0.2-2.2) rates again same between DSM-IV and ICD-10.

There were no cases of hypomania/mania reported.

6.8.2.6 **Pan et al. 2014 (conducted 2009-2011, Brazil).**

This Brazilian study screened for lifetime prevalence of manic symptoms by interviewing the main caregiving parent of two thousand five hundred twelve 6 – 12-year-old children with the parent-version of the DAWBA. The authors describe their sampling methodology:

> In the screening phase, 9,937 parents of 6- to 12-year-old children were interviewed using the Family History Survey (FHS). Using a simple randomisation procedure, we selected 2,512 subjects for further assessment: a high-risk subgroup (n = 1,554) and a random-selection group (n = 958). (p. 626)

Consideration of this sampling led to the slightly lower weighted prevalence rates listed in Figure 6.3 (P. Pan, 2019, email, 15 March). Impairment was measured using the impact score on the SDQ and the parents were interviewed about parental psychopathology with the Mini International Psychiatric Interview (MINI).

Pan et al. found 479 (19.1%) of the 2,503 subjects screened positive for lifetime manic symptoms and five children (0.2%), mean age 9.4 years ± 1.34 years, met criteria for lifetime Bipolar-I/Bipolar-II, while a further 41 subjects (1.6%) met criteria for Bipolar-NOS.

Other psychiatric disorders lifetime prevalence rates for the whole sample of 2,503 were: any disorder 25.7%, any anxiety disorder 9.9%, any depressive disorder 2.9%, ADHD 10.9%, any CD/ODD 6.8%. For the 479 who had screened positive for lifetime manic symptoms the comorbidity was higher: any disorder 43.6%, any anxiety disorder 18.4%, any depressive disorder 6.3%, ADHD 19.8%, any CD/ODD 11.9%.

Pan et al. also examined two dimensions of manic symptomatology drawn from the DAWBA: 1) an 'under-control' subscale including irritable, distractible, risk taking, less self-control, poor concentration, invades other people's personal space, bossy, less concerned about getting into trouble, overly sexed, constant changes of plans and activities, flight of ideas, talking to strangers, overconfident, and restless; 2) an 'exuberant' subscale including cheerful, joking and laughing more than usual, outgoing, active, fast talk, noisier, gets more done, full of energy, excitable, and restless. Only the 'under-control' subscale was associated with psychiatric morbidity and psychosocial impairment, and with severe symptoms in the 'episodes of going abnormally high' domain in the DAWBA, whereas the 'exuberant' subscale was associated with mild symptoms. In multivariate analysis the 'under-control' subscale predicted six domains of parental psychopathology including mania whereas the 'exuberant' subscale did not predict any.

Also, the parents of 'under-control' children reported moderately high rates of their own lifetime psychopathology: e.g. 9.1% mania, 31.3% major depression, 34% any anxiety disorder. Using latent class analysis (LCA), Pan et al. found "manic symptoms are associated with genetic loading for mood disorders in general and BD in particular" (p. 631).

The authors commented that the 'exuberant' episodic manic symptoms being mild and not associated with impairment may need to be severe and frequent to be of significance. They note that:

> [S]everal under-control symptoms of mania are also symptoms of ADHD and ODD/CD. Therefore, we may have ascertained symptoms of externalizing disorders rather than manic symptoms. (p. 631)

However, the DAWBA does specifically ask that these symptoms occur episodically. They also comment on the similar methodology and findings to Stringaris, Santosh et al. (2010) (one of the original 12 epidemiological studies), who found very low rates of Bipolar-I/Bipolar-II and a larger group of Bipolar-NOS children/youth who may or may not progress to bipolar disorder proper. In their contribution to the *CAMH* debate on PBD, Pan, Salum and Bressan (2019) state:

> BD-NOS prevalence was 1.6% in the Brazilian sample, compared to 1.1% by parent report and 1.5% by youth report in the British B-CAMHS (Pan et al., 2014; Stringaris et al., 2010). We have also found that overall BD prevalence was 1.8% in the [Brazilian] study, exactly the same prevalence rate reported in Van Meter et al. (2011) metanalysis. This result adds to the pool of non-US studies in which youth BD could be identified using both narrow (0.2%) and broad (1.6%) criteria. However, this finding does not necessarily mean that all these subjects are 'true' bipolar cases. (p. 104)

Pan, Salum and Bressan questioned the PBD hypothesis based on 'broad criteria' further. In the same article they add:

> [U]ntil we do fully understand the pathophysiology of BD, impairment may help guide our judgement when we face the hard task of distinguishing manic symptoms from normative (and perhaps developmentally essential) exuberant and under-controlled behaviour in youth. (p. 104)

Therefore, the authors of both the Brazilian and British studies, in analysing the data, came to the conclusion that Bipolar-NOS or soft bipolar spectrum cases, which would include PBD hypothesis cases, were unlikely to be related to DSM/ICD Bipolar-I/Bipolar-II.

6.8.2.7 **Vizard et al. 2018 (conducted 2017, England).**

This recent English study:

> [W]as funded by the Department of Health and Social Care, commissioned by NHS Digital, and carried out by the National Centre for Social Research, the Office for National Statistics and Youthinmind. (NHS Digital 2018a, para. 4)

It surveyed nine thousand one hundred seventeen 2 – 19-year-old children and young people (a 52% response from 18,029 randomly selected). The Development and Well-Being Assessment (DAWBA) was used and informants were parents only for 2 – 10-year-olds; parents, teachers and child/young person for 11 – 16-year-olds; and parent and young person for 17 – 19-year-olds (Vizard, Sadler et al. 2018, p. 6). The numbers interviewed were:

> 8,602 productive parent interviews were achieved in total. When split by age group 1,463 parent interviews were achieved for 2 to 4 year olds, 3,597 were achieved for 5 to 10 year olds and 3,121 were achieved for 11 to 16 year olds. A further 2,609 interviews were achieved with 11 to 16 year olds. For 17 to 19 year olds, 936 interviews were achieved with the young person and 421 interviews were achieved with their parent. ...
>
> Of the 6,718 interviews conducted with parents of 5 to 16 year olds, 6,665 were eligible for teacher consent. Of these, 5,930 (89%) consented to the teacher questionnaire, 5,718 (86%) were invited to take part, and 3,595 (54%) returned a completed questionnaire. (p. 45)

Trained lay interviewers conducted the interviews and clinician raters made the diagnoses. The DAWBA question for hypomania/mania is item M2H8: “Has he or she had episodes in the past where he/she has gone ‘high’ instead of ‘low’? If so, please describe.” For the youth, the same wording is used but commencing “Have you had ...”, the question is omitted from the teacher DAWBA. The interviewer is instructed to explore in depth if the answer is yes, with questions about description of, time course, severity of symptoms, level of impairment and family understanding of the problem.

The DAWBA delivers ICD-10 diagnoses, and from the data provided the clinical rater might give a diagnosis of manic/hypomanic episode (F-30 codes) or, if recurrent an F-31 code diagnosis that includes BD-I to BD-II (F-31.0 – F31.8) and Bipolar-unspecified (F-31.9)

disorders. Thus, the MHCYP study did not define the type of bipolar disorder detected, the study stated:

> Children with mania/bipolar affective disorder were counted as having an emotional disorder, however these disorders are not examined in isolation in this topic report due to the small proportion of children identified (less than 0.1%). (Vizard, Pearce et al. 2018)

The study reported (NHS Digital 2018b) zero cases (to the first decimal place) amongst all 5 – 17-year-olds. However, when broken down by gender and age group the prevalence rate was 0.1% amongst 17 – 19-year-olds, which was all amongst older female youth (0.3%) and no older male youth (0.0%). Additionally, 0.1% of the 11 – 16-year-old boys were reported as having mania/bipolar disorder.

However, personal email communication with authors Tim Vizard and Tamsin Ford (7 May 2019) indicated a rate of mania/BD among the seven thousand six hundred fifty-four 5 – 17-year-old children and youth of 0.04% and no child or adolescent under the age of 16-years-old had an ICD-10 F30 or F31 bipolar spectrum disorder.

If the rates are averaged for 7,654 children and youth in the 5 – 19-year-old range then they were (with 95% CI): All: rate of 0.0% (0.0 – 0.1), boys: 0.0% (0.0 – 0.1), girls: 0.1% (0.0 – 0.2). In comparison the rates for any anxiety disorder was: All: 7.2% (6.6 – 7.9), boys: 5.4% (4.7 – 6.2), girls: 9.1% (8.1 – 10.1). For any depressive disorder: All: 2.1% (1.7 – 2.5), boys: 1.4% (1.0 – 1.8), girls: 2.8% (2.2 – 3.5). Disorders increased with age, for instance 20.3% and 6.5% of older adolescent girls were recorded as having an anxiety or depressive disorder respectively. These rates could be considered low in comparison to some other nations such as the US. The authors note a limitation was the response rate of only 52% to the stratified random selection across England.

6.8.2.8 **Karacetin et al. 2018 (conducted 2014-2015, Turkey).**

This Turkish study had a large number of co-authors representing 44 Turkish child and adolescent psychiatry departments and drew upon data from The Epidemiology of Childhood Psychopathology in Turkey (EPICPAT-T) Study. The subjects were 5,842 primary school students from the second, third and fourth grades with a mean age of 8.7-years-old (S.D. =

1.2). Parents were interviewed with the Turkish translation of the semi-structured interview, the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version (K-SADS-PL). The focus of this study was the prevalence of affective disorders. The authors noted that the K-SADS-PL affective disorders component covered the full gamut of bipolar spectrum disorders:

> [M]anic bipolar disorder, depressed bipolar disorder, mixed bipolar disorder, rapid cycling bipolar disorder, hypomania, cyclothymia, bipolar disorder not otherwise specified (BPNOS) and schizoaffective disorder-manic type. (p. 517)

However, they did not discover a single case. They attributed the lack of bipolar spectrum disorders to the younger age of this primary school cohort, comparing it to the absence of mania in the Great Smoky Mountains Study in the US (Costello et al. 1996) and stated:

> Consistent with these findings, there were no cases of BP disorder in our study sample, in which school-age children with a mean age of 8.7 ± 1.2 years were included. (p.519)

The Turkish authors postulated that "different assessment instruments may also contribute to differences in prevalence" and cited "another study from Turkey, where Young Mania Rating Scale was used to screen 2,468 school age children (7 – 12 years of age), prevalence of BP was found to be 1.1% (Diler et al. 2008)" (p. 519). The lead author of that other Turkish study, Rasim Diler, is a Turkish-American psychiatrist who is affiliated with the University of Pittsburgh. Karacetin and colleagues in the next sentence cite a study from the Pittsburgh group to say:

> Due to ongoing debate on the phenomenology of BP in youth, studies may use diagnostic criteria for either narrow or broad phenotype BP, which may have an impact on prevalence rates. For example, when sub-syndromal cases were included, lifetime prevalence of BP was found to be as high as 5%. (Sala et al., 2009). (p. 519)

Karacetin et al. continue to discuss the "challenges clinicians face while screening BP in youth" due to developmental constraints, symptom overlaps with other disorders and variability in symptom expression. They note that "irritability can be a part of many psychiatric disorders"

and that “the prevalence of ADHD in the EPICPAT-T Study was found to be 12.4% … some of the cases with BP might have been misdiagnosed as ADHD” (p. 519).

The prevalence of depressive disorders in this study was (with/without impairment): All depressive disorders 2.5%/1.6%; major depressive disorder 1.06%/1.7%; dysthymia 0.2%/0.2%; adjustment disorder with depressive features 0.4%/0.17%; depressive disorder NOS 0.15%/0.14%. In context of these relatively low prepubertal affective (depressive) disorder prevalence rates, the absence of hypomania/mania episodes is plausible though some false negatives may be obscured by the high ADHD rate as the authors suggest.

6.8.3 **Discussion**

This updated meta-analysis by Van Meter and colleagues provides a total now of 19 (20 including the NZ survey) of the best epidemiological surveys in the adolescent population, with newer surveys adding more community prevalence data in the pre-adolescent population. As described above, a detailed narrative review provides more accurate information than a meta-analysis of such heterogeneous methodologies and results. From the updated list of surveys, further observations can be deduced and are elaborated here.

6.8.3.1 **The NZ birth cohort data**

Van Meter, Moreira and Youngstrom (2019b) said they removed the New Zealand study (Kim-Cohen et al. 2003):

> [B]ecause the pediatric bipolar disorder rate was based on retrospective report about childhood onset using interviews with adults; thus, the retrospective period varied in length and typically spanned decades. (p. e3)

This still gives the impression the adults were retrospectively reporting pre-age 18 bipolar disorder.

In our reanalysis of the original 12 studies (Parry, Allison & Bastiampillai 2018a; Appendix A31; this chapter), we described the NZ birth cohort studies in some detail. Bipolar disorder (not specified whether Bipolar-I or Bipolar-II) rates of 2% at age 21 and 3% at age 26 were reported. Our reading of a series of articles from the NZ group was that no bipolar disorder

diagnoses were made up to age 18, not even in the retrospective data reported in the Kim-Cohen et al. (2003) article.

6.8.3.2 **Discrepant informant data**

In their discussion, Van Meter, Moreira and Youngstrom (2019b) address the discrepant informant reports to questionnaires. This was one of the points we highlighted in our 2018 reanalysis. One of the glaring indications of this was the Dutch study (Verhulst et al., 197) where there was no concordance at all as to the presence of Bipolar-I/Bipolar-II between youth (1.8%) and parent (1.2%) report. In their original meta-analysis, Van Meter, Moreira and Youngstrom (2011) added the youth and parent reports in the Dutch survey to derive a prevalence rate of 2.8%. However, if prevalence were to be based on parent and youth concordance, then the rate was 0%.

In their updated meta-analysis Van Meter and colleagues chose to utilise the parent report (1.2%) rate only. They noted they chose the parent report only also for the British survey (Stringaris, Santosh et al., 2010) and have updated the data in their meta-analysis to note the parent report for Bipolar-I/Bipolar-II is just 0.1%. They cite a figure of 1.2% for bipolar spectrum disorder, which combines this result with the 1.1% prevalence for BD-NOS on parent report.

Van Meter, Moreira and Youngstrom (2019b) cite their group's own research on caregiver, youth and teacher rating scales (Youngstrom et al. 2015) that parent report is more reliable for prioritising parent over youth report. Nonetheless, they acknowledge that "best practice guidelines suggest integrating information from multiple informants" (p. e8). Yet this obscures the fact that there was zero agreement between youth and parent in the Dutch survey. There was similar low kappa scores and low concordance in all the epidemiological surveys that had more than one informant.

In total, 8 out of 19 of the epidemiological studies had both parent and youth informants. In addition to the Dutch and British studies, four of these studies methodologies gave low prevalence rates. The Irish study (Lynch et al. 2006) reported zero cases of bipolar spectrum disorders. The more recent Brazilian study (Anselmi et al. 2010) reported zero cases of Bipolar-I. The US Great Smoky Mountains study (Costello et al. 1996) zero cases of Bipolar-I

and a 0.1% 3-month prevalence of Bipolar-II. There was just a single adolescent case of mania for a Bipolar-I rate of 0.7% in the US Missouri study (Kashani et al. 1987) when impairment criteria were accounted for (Carlson & Kashani 1988). In contrast, the remaining two US studies gave high rates by adding parent and child report rates: Gould et al. (1998) found a Bipolar-I rate of 1.2% and Kessler et al. (2009) a Bipolar-I rate of 0.5% (based on K-SADS) or 1.0% (based on CIDI), and total bipolar spectrum rate of 6.3% (K-SADS) 6.6% (CIDI). The level of concordance or kappa value are not revealed, so the validity of these high rates is open to speculation.

6.8.3.3 **Bipolar disorder very rare in pre-adolescent children**

Van Meter, Moreira and Youngstrom (2019b) note that "older minimum age was associated with higher rates (*P* <.0001)" (p. e6). This observation was more robust in the updated meta-analysis as whereas only three of the original epidemiological studies had children under age 12, five of the newer eight studies did.

In two of the original studies (Costello et al. 1996; Gould et al. 1998) age of those who met bipolar spectrum criteria were not given. Neither was age given of the single case of Bipolar-I/Bipolar-II amongst three thousand six hundred eighteen 8 – 15-year-olds (0.028%) in the British Stringaris, Santosh et al. (2010) study, and the authors did not consider this a "definite" (p. 33) case as it lacked parent and youth concordance.

Of the five newer surveys with children under age 12, the two Brazilian studies (Anselmi et al. 2009; Pan et al. 2014) and the English study (Vizard, Sadler et al. 2018) all use the DAWBA instrument and thus comparable methodology to Stringaris, Santosh et al. (2010). Anselmi et al. (2009) found no cases of bipolar spectrum disorder amongst four thousand four hundred forty-eight 11 – 12-year-old children. Pan et al. (2014) found five cases of Bipolar-I/Bipolar-II among two thousand five hundred twelve 6 – 12-year-olds for a rate of 0.2%, this held true for four cases out of 2,108 for the weighted prevalence. As described above it was doubtful as to whether the 42 Bipolar-NOS cases for a 1.7% Bipolar-NOS prevalence were truly part of a bipolar disorder spectrum. The large English study of Vizard, Sadler et al. (2018) found no cases of bipolar spectrum disorder (ICD-10 F-30/F-31 codes) under age 16. It is also probable that most of the 10 to 13 cases of hypomania/mania detected with the DISC-IV among the four thousand one hundred seventy-five 11 – 17-year-olds in Texas (Roberts RE, Roberts &

Xing 2007) would have been in the adolescent age range. There were zero cases of bipolar spectrum disorder detected with the K-SADS-PL among the five thousand eight hundred forty-two Turkish 7 – 10-year-olds (Karacetin et al. 2018).

6.8.3.4 **Adolescent hypomania generally not progressing to adult bipolar disorder**

The majority of bipolar spectrum cases across the 19 (20 with the NZ survey) studies were of adolescents and mostly by self-report. The validity of these diagnoses is thrown into some question by two of the newer studies (Tijssen et al. 2010b; Päären et al. 2014) that incorporated follow-up interviews some years later. Although the German study of Tijssen et al. (2010b) excluded baseline lifetime cases of bipolar disorder, it did not find any new cases of bipolar disorder over the ensuing 8 years, despite the presence of hypomanic symptoms in some subjects and the focus of the study being on emerging affective symptoms.

In a second article (Tijssen 2010a), the authors reported on a larger cohort (*n* = 1,565) from the same study that involved not only adolescents aged 14 – 17-years at baseline but included 18 – 24-year-olds. Over the 10-year follow-up period they found that meeting criteria for a DSM-IV hypomanic/manic episode correlated to a higher number of hypomanic/manic symptoms and persistence of symptoms over follow-up assessments. However, while 25% of the cohort experienced hypomanic/manic symptoms at any of the three assessment times, the overall risk of developing a hypomanic/manic episode was much lower: "2.4%" for persistence of symptoms and "1.2 – 1.9%" with increasing number of symptoms (p. 105). Tijssen et al. (2010a) concluded:

> In a substantial proportion of individuals, onset of clinical bipolar disorder may be seen as the poor outcome of a developmentally common and usually transitory non-clinical bipolar phenotype. (p. 102)

Similarly, the 15-year follow up in the Swedish study (Päären et al. 2013) indicated that only a small percentage of adolescents who met criteria for "hypomania spectrum disorder" developed Bipolar-I (3%) or Bipolar-II (6%) by their early 30s.

These findings urge caution on diagnosing bipolar disorder in adolescents and even young adults on the basis of cross-sectional assessment of hypomanic symptoms that fail to meet DSM or ICD criteria for a full hypomanic/manic episode.

The validity of bipolar spectrum diagnoses in younger Americans was also brought into question by an article titled “Are there developmentally limited forms of bipolar disorder?” (Cicero, Epler & Sher 2009; Chapter 4.8.2.18). Data from the U.S. National Epidemiological Survey on Alcohol and Related Conditions (NESARC) study showed that as people grew older, decreasingly fewer individuals reported either a 12-month or lifetime prevalence of bipolar spectrum disorders. The decline was steady with advancing age, with just over 4% of 18 – 20-year-olds meeting NESARC criteria for a bipolar spectrum diagnosis but only 0.5% of those aged 60 and older (Cicero, Epler & Sher 2009). This was counter-intuitive if bipolar disorder is a lifelong illness and not over-diagnosed in youth due to the mood lability exhibited by many in their teenage years.

6.8.4 **Conclusion to re-analysis of updated meta-analysis**

The eight additional epidemiological surveys led Van Meter, Moreira and Youngstrom (2019b) to increase, by meta-analytic statistical analysis, their community prevalence finding for PBD from 1.8% to 3.9%. However, a narrative review of the same surveys builds upon the findings of the reanalysis of the first dozen surveys and finds the data to more persuasively support the classical perspective that hypomania/mania is exceedingly rare prior to puberty. Further, it appears from follow-up data that hypomania is overdiagnosed in surveys of adolescents.

CHAPTER 7. LITERATURE REVIEW: GEOGRAPHY OF PBD 2016[2]

7.1 Introduction: To what extent has the PBD literature expanded beyond the US

The proposed PBD phenotypes arose originally from just two US academic centres (Wozniak, Biederman, Kiely, et al. 1995; Geller et al. 1995), and appeared to spread out from these starting points of St Louis, Missouri and Boston, Massachusetts, to the rest of the US and then to the rest of the world. However, one of the key issues with the PBD hypothesis is that it remains predominantly a US theory and practice: one way of examining this is through tracking the extent to which these landmark articles were subsequently cited in the literature.

In addition, the two prominent '10-year review articles on PBD' in *JAACAP* (Geller & Luby 1997; Pavuluri, Birmaher & Naylor 2005) were also likely to have been cited, given their scope and prominence.

Therefore, I examined how these four seminal PBD articles have been cited in the years since their publications. Specifically, I examined how the articles were cited internationally.

7.2 Methodology: *Web of Science* database and search engine

The *Web of Science* database "is most visible for the worldwide scientific community and therefore most likely to be cited" (Lariviere & Grant 2016, p. 1). The *Web of Science* bibliographic records included titles, author names, abstracts, key words, and citing papers. This method of examining literature gives insights into the co-authorship networks and the places of origin of articles on a topic. The 'citation tree' of citing articles is not a comprehensive collection of articles on a topic, but rather a representative sample of articles that have cited seminal articles on a topic.

[2] *This chapter includes passages that have been published (Parry et al. 2019b; Appendix A35).*

7.2.1 Step 1: Search for four seminal PBD articles and citing articles

On 27 September 2016, the four articles had the following number of citations: Geller et al. (1995): 196; Wozniak, Biederman, Kiely et al. (1995): 474; Geller and Luby (1997): 331; Pavuluri, Birmaher and Naylor (2005): 189. When the four searches were combined the total number of citations, taking into account overlapping citations, was 830 articles. The same search conducted on 21 January 2014 had found a total of 791 articles. Sorting through both sets of articles several duplicate articles were discovered and some from the earlier search that had been missed in the second search. Accounting for these the full total was 835 articles.

7.2.2 Step 2: Analysis of citation tree by categories

The citing articles were sorted according to the following fields: *authors*; *source titles* (e.g. journals publishing the articles); *organizations* (institutions affiliated with the authors); *countries* (of the authors/affiliated institutions); and *publication year* (of the articles). In particular, results were collated to analyse the number of articles and authors from the US compared with other countries. Examination of the co-authorship of articles shed light on collaborating networks of researchers and institutions.

7.2.3 Step 3: Ascertain each article's perspective on PBD

A key question was what perspective each article took. Whether authors were:

1. agreeing with the PBD hypothesis
2. sceptical of the validity of the PBD hypothesis
3. holding to the traditional view that bipolar disorder has a late-adolescent to early-adult-onset, without overtly expressing scepticism about PBD, or
4. were about SMD/DMDD as an alternative descriptor for severe irritability.
5. were defined as 'not applicable', where the article was not about bipolar disorder in children or youth from a bipolar disorder aspect but had nonetheless cited one of the four seminal PBD articles.

Thus the 835 articles were read to assess perspective on PBD. *Web of Science* gives the abstracts for all articles. If the article's perspective was not clear from the abstract, then the full article was read. The articles were then assigned as either: "Pro-PBD"; "Sceptical"; "SMD"; "Traditional"; "NA". The country of origin and affiliated institution of the authors could then

be compared with these perspectives. All 835 articles, with abstracts and assignation as to perspective on PBD, are listed in Appendix C (divided into three groupings: C1: only US authors; C2: US authors plus international co-authors; C3: only non-US authors).

7.2.4 Examples of each perspective

1. Pro-PBD perspective:

Record 41 of 50 = PRO

Title: Recognizing and managing bipolar disorder in children

Author(s): Wozniak, J

Source: JOURNAL OF CLINICAL PSYCHIATRY **Volume:** 66 **Pages:** 18-23 **Supplement:** 1 **Published:** 2005

Abstract: Bipolar disorder affects people of all ages, including preschool-aged children. Two major difficulties in diagnosing children with bipolar disorder are its overlap with attention-deficit/hyperactivity disorder (ADHD) and its developmentally distinct presentation from that in adults, with high rates of irritability, chronicity, and mixed states. Comorbid conditions are common in bipolar disorder and, in addition to ADHD, include depression, anxiety disorders, oppositional defiant disorder, and conduct disorder. Family studies have helped to confirm the validity of bipolar disorder in children. In terms of treatment, children do not appear to respond well to conventional mood stabilizers alone. However, using an atypical antipsychotic either alone or in addition to another mood stabilizer has shown utility in treating manic symptoms, depression in mixed states, and aggression. Amphetamine salts have been helpful in treating bipolar children with comorbid ADHD, but no data are available on treating comorbid depression in bipolar children. Because childhood-onset mania is commonly chronic rather than episodic, highly comorbid, and characterized by high rates of irritability, future clinical trials should examine the overlap of mania with other disorders in children to determine routes to accurate diagnosis and treatment.

2. Sceptical perspective:

Record 35 of 50 = SCEP (FRANCE)

Title: Attention deficit-hyperactivity disorder or juvenile mania

Author(s): Vantalon, V; Cohen, DM

Source: ARCHIVES DE PEDIATRIE **Volume:** 11 **Issue:** 12 **Pages:** 1484-1489 **DOI:** 10.1016/j.arcped.2004.09.021 **Published:** DEC 2004

Abstract: In recent years, the relationship between juvenile mania and attention deficit hyperactivity disorder has been the focus of renewed clinical research and controversial debates. We have reviewed the recent literature about bipolar disorder and juvenile mania in children in order to clarify the knowledge in assessment, phenomenology and diagnosis of prepubertal bipolar disorder. Despite the fact that prepubertal mania has been recognized, there is no consensus on the diagnostic criteria. The symptomatic overlap and comorbidity of juvenile mania with attention deficit hyperactivity disorder has produced confusion. As prospective studies are not yet contributive because of the heterogeneity of samples and criteria, one cannot consider these manic children as truly cases of bipolar disorder.

3. SMD related:

Record 21 of 50 = SMD (USA, BRAZIL, ENGLAND)

Title: Irritability in children and adolescents: past concepts, current debates, and future opportunities

Author(s): Krieger, FV; Leibenluft, E; Stringaris, A; Polanczyk, GV

Source: REVISTA BRASILEIRA DE PSIQUIATRIA **Volume:** 35 **Pages:** S32-S39 **DOI:** 10.1590/1516-4446-2013-S107 **Supplement:** 1 **Published:** 2013

Abstract: Irritability is defined as a low threshold to experience anger in response to frustration. It is one of the most common symptoms in youth and is part of the clinical presentation of several disorders. Irritability can present early in life and is a predictor of long-term psychopathology; yet, the diagnostic status of irritability is a matter of intense debate. In the present article, we address two main components of the debate regarding irritability in youth: the misdiagnosis of chronic irritability as pediatric bipolar disorder, and the proposal of a new diagnosis in the DSM-5, disruptive mood dysregulation disorder, whose defining symptoms are chronic irritability and temper outbursts.

4. Traditional perspective, without overt scepticism or discussion of PBD hypothesis:

Record 2 of 50 = TRAD (FRANCE)

Title: Adolescent manic-depressive disorders: Clinical aspects

Author(s): Balsan, G; Corcos, M

Source: ARCHIVES DE PEDIATRIE **Volume:** 23 **Issue:** 4 **Pages:** 417-423 **DOI:** 10.1016/j.arcped.2015.12.006 **Published:** APR 2016

Abstract: More than 50% of bipolar disorders diagnosed among adults first appeared before the age of 18. It is well established that adolescence is the high-risk period for the onset of major mood episodes associated

with bipolar disorders. Even though there are few early-onset bipolar disorders, they are very severe. The most robust risk factor predicting bipolar disorder is a positive family history. Morbidity, mortality, and suicidality are high and have a severe impact on overall functioning, professional integration, family life, and affective relationships. Improving diagnosis of early symptoms should ameliorate these patients' prognosis.

5. Not Applicable to bipolar disorder in children and adolescents:

Record 14 of 50 = NA (CANADA)

Title: A model of communicative perspective-taking for typical and atypical populations of children

Author(s): Nilsen, ES; Fecica, AM

Source: DEVELOPMENTAL REVIEW **Volume:** 31 **Issue:** 1 **Pages:** 55-78 **DOI:** 10.1016/j.dr.2011.07.001 **Published:** MAR 2011

Abstract: Successful communication requires that individuals attend to the perspective of their conversational partners and use this information to modify their behavior accordingly. This paper presents a framework by which to understand children's communicative perspective-taking skills and, within this framework, outlines three routes by which children's communicative perspective-taking performance can be disrupted. First, children may have difficulty in communicative contexts due to deficits in mentalizing ability whereby they are unable to appreciate another's perspective. Second, children may have intact mentalizing abilities but do not have the cognitive skills to support the use of this information when generating communicative behaviors. Third, decreased social exposure may lead to exacerbated deficits in either mentalizing ability or the use of mentalistic information within communicative contexts. Patterns within both typical and atypical populations (i.e., autism, ADHD, and mood disorders) are reviewed.

For further analysis, I excluded the 48 articles that were NA. The 787 remaining relevant articles were then analysed, according to the affiliation and nationality of authors, publishing journals and perspective towards the PBD hypothesis.

7.2.5 Publication and presentation of this literature review

I presented the data at the FCAP of the RANZCP annual meeting in Hobart on 3 October 2016. This chapter formed the basis for a manuscript with my co-authors Stephen Allison and Tarun Bastiampillai which has subsequently been published in the journal *Clinical Child Psychology and Psychiatry* (Parry, Allison & Bastiampillai 2019b; Appendix A35).

7.3 Results

The US authorship within the citing articles comprised 79% of the total. There were 551 articles authored by only US affiliated authors (70%), 73 articles with US and international co-authors (9%) and 163 articles with solely non-US authors (21%). Of the academic institutions authors were affiliated with, 30 of the 34 institutions from which at least 10 articles came were in the US, while 143 of the 174 authors with at least four articles were affiliated with US institutions (full list in Appendix C4).

7.3.1 Main affiliated institutions of publishing authors

Although co-author affiliations exaggerate the number of articles in the citation tree when sorted by institution, the institutional affiliation of articles provides information of where academic interest in the PBD hypothesis has been located (Parry, Allison & Bastiampillai 2019b; Figure 7.1). Biederman, Wozniak and colleagues from Boston had continued to publish prolifically (248 articles from MGH-Harvard) in support of the 'broad phenotype' PBD hypothesis.

The 'narrow phenotype' PBD hypothesis originally from Geller and colleagues at WUSL, Missouri (33 articles) has been merged with Bipolar-NOS in the continuing research of the COBY study group comprising Birmaher, Axelson and colleagues at the University of Pittsburgh, Pennsylvania (57 articles). Amongst the citing articles, an early article from the COBY group, "Clinical course of children and adolescents with bipolar spectrum disorders" (Birmaher et al. 2006), had 597 citations on Google Scholar as of 20 March 2018.

The University of Cincinnati (63 articles), Case Western Reserve University (54 articles), Cincinnati Children's Hospital (21 articles) and Ohio State University (21 articles), all in Ohio, reflected the work of several authors (e.g. Kowatch, DelBello, and Findling) who were lead authors in the heavily cited seminal PBD article: "Treatment guidelines for children and adolescents with bipolar disorder" published in *JAACAP* in 2005 (Kowatch et al. 2005) that has 564 citations (Google Scholar, 20th March, 2018).

Other prominent US PBD research institutions included: University of North Carolina (37 articles), reflecting the work of Youngstrom and colleagues; University of Illinois (36 articles)

reflecting the work of Pavuluri and colleagues; and Stanford University (32 articles) reflecting the work of Chang and colleagues.

The four non-US institutions that made this list reflect the collaboration of authors at Kings College London with the NIMH regarding SMD/DMDD; of US author Akiskal with colleagues at the University of Pisa, Italy; of Canadian PBD researcher Goldstein (University of Toronto) with colleagues at Pittsburgh University; and of sceptical perspective articles by Duffy and colleagues from Dalhousie University, Canada.

Institution	**Articles**	**non-USA**
Harvard University	137	
Massachusetts General Hospital	111	
University of Cincinnati	63	
University of Pittsburgh	57	
Case Western Reserve University	54	
National Institute of Mental Health (NIMH)	42	
University of California Los Angeles	37	
University of North Carolina	37	
University of Illinois	36	
Washington University in St Louis	33	
Stanford University	32	
State Univ. of New York Stony Brook	27	
State Univ. of New York Upstate Medical University	22	
Cincinnati Children's Hospital	21	
Ohio State University	21	
University of Texas	20	
Yale University	17	
Mclean Hospital	16	
Kings College London	15	England
University of California San Diego	15	
Brown University	14	
Columbia University	14	

Johns Hopkins University	14	
University of Pisa	14	Italy
Massachusetts Mental Health Center	13	
University of Colorado	13	
University of Pennsylvania	13	
University of Toronto	13	Canada
George Washington University	12	
New York University	12	
Cleveland Clinic	10	
Dalhousie University	10	Canada
University of Washington	10	

Figure 7.1: The institutions with at least 10 citing articles (Parry, Allison & Bastiampillai 2019b, p. 7). Reproduced with permission.

7.3.2 Main journals publishing the citing articles

Fifty-four percent of citing articles were published in nine US-based journals (Parry, Allison & Bastiampillai 2019b; Figure 7.2). The *JAACAP* led the list (92 articles), ensuring a wide readership among US child and adolescent psychiatrists. Leading PBD researchers on *JAACAP*'s editorial board include DelBello, Goldstein and Frazier. Second ranked was the *Journal of Affective Disorders* (78 articles), whose editor-in-chief since 1996 is Professor Hagop Akiskal. Other top journals included *Bipolar Disorders* (59 articles), the journal of the ISBD, where Professor Melissa DelBello is the "field editor" for "pediatric bipolar disorder"; *The Journal of Child and Adolescent Psychopharmacology* (51 articles), with Professor Kiki Chang as editor for bipolar disorders, DelBello for neuroimaging oversight, and Pavuluri on the editorial board; the *Journal of Clinical Psychiatry* (41 articles), which is the journal of the American Society for Clinical Psychopharmacology, with a website that includes extensive pharmaceutical industry advertising, its editorial board is not readily apparent; and *Biological Psychiatry* (41 articles) which has the third highest impact factor of 135 psychiatry journals, 101 of its 111 editorial board members are from the US and include Luby and (until recently) Geller from WUSL; the *American Journal of Psychiatry* (24 articles); and *Child and Adolescent Psychiatric Clinics of North America* (23 articles).

The *Canadian Journal of Psychiatry*, (13 articles) was the only non-US journal in the top 10. The 13 articles reflected the mainly sceptical perspective articles of Duffy and colleagues as well as several traditional perspective articles from India. *Development and Psychopathology* is a US based journal with a large almost solely US editorial board, although no prominent PBD researchers.

Journal	**Articles**	**% of 787**	**Country of origin**	**H index (Impact Factor) 2017**
Journal of the American Academy of Child and Adolescent Psychiatry	92	11.7%	US	212 (6.250)
Journal of Affective Disorders	78	9.9%	US	158 (3.786)
Bipolar Disorders	59	7.5%	Internat.	113 (4.490)
Journal of Child and Adolescent Psychopharmacology	51	6.5%	US	76 (2.901)
Journal of Clinical Psychiatry	41	5.2%	US	183 (4.247)
Biological Psychiatry	41	5.2%	US	283 (11.982)
American Journal of Psychiatry	24	3.0%	US	318 (13.391)
Child and Adolescent Psychiatric Clinics of North America	23	2.9%	US	62 (1.798)
Canadian Journal of Psychiatry	13	1.6%	Canada	99 (3.612)
Development and Psychopathology	13	1.6%	US	151 (4.357)

Figure 7.2: The top 10 journals for this citation tree search (Parry, Allison & Bastiampillai 2019b, p. 5). Reproduced with permission.

7.3.3 Perspectives of citing articles

The perspectives of the 787 articles were rated as follows: 586 (74%) pro-PBD, 70 (9%) sceptical of PBD; 100 (13%) focusing on traditional perspectives of bipolar disorder in youth;

27 (3%) focusing on SMD/DMDD, and 4 (0.5%) articles attempting 'consensus' on the subject of the PBD hypothesis (Figure 7.3).

	Pro	Scep	Trad	SMD/DMDD	Cons	Total
US alone	461	33	35	19	3	551
US + international	60	7	2	3	1	73
Non-US	65	30	63	5	0	163
Total	**586**	**70**	**100**	**27**	**4**	**787**

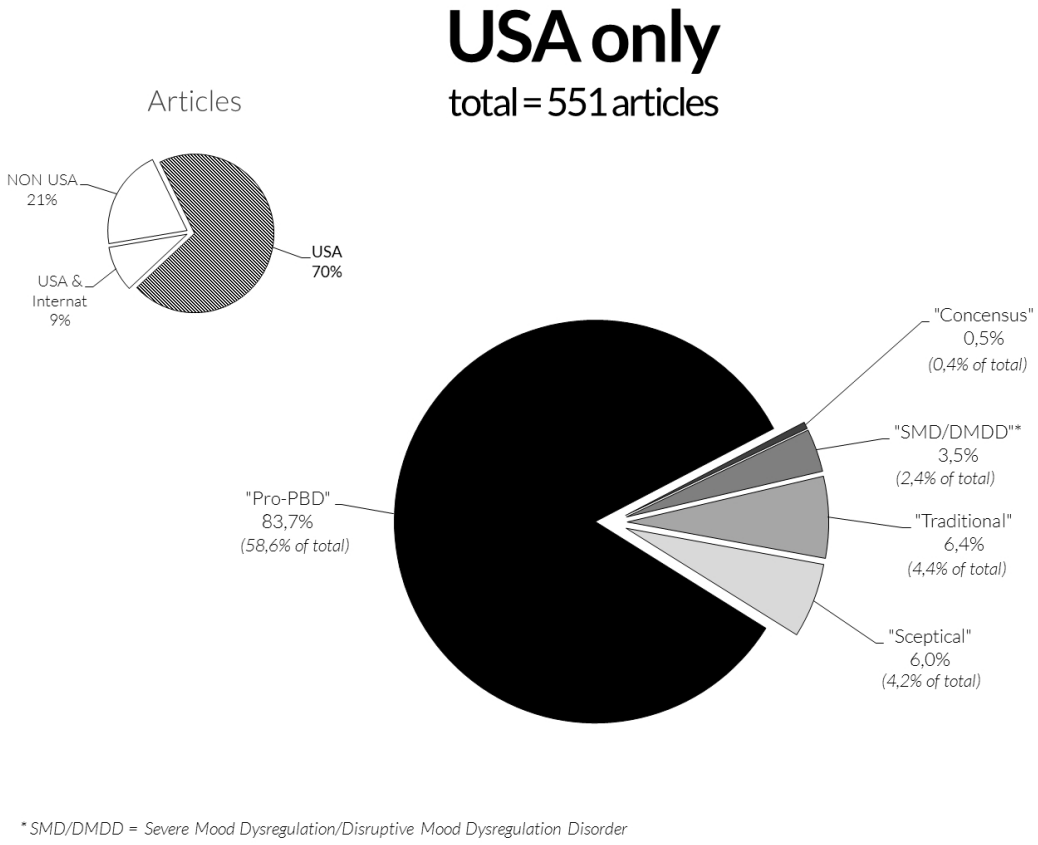
Pro = pro-PBD, Scep = sceptical, Trad = traditional, SMD/DMDD = Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder, Cons = consensus.

Figure 7.3: Perspectives of the citing articles by geographical location of authors' affiliated institutions

These perspectives are further illustrated in Figures 7.4, 7.5 and 7.6.

7.3.3.1 **Perspectives of articles from the US alone.**

The pro-PBD hypothesis perspective dominated with nearly 83.7% of the US articles. The rates of sceptical, SMD/DMDD related, and traditional, articles are illustrated in Figure 7.4. There were 3 articles that sought a 'consensus' perspective including two articles under the auspices of AACAP (McClellan et al. 2007; Carlson, Findling et al. 2009).



** SMD/DMDD = Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder*

Figure 7.4: Breakdown of perspectives in US published articles

7.3.3.2 **Perspectives of articles with co-authors from the US plus other countries.**

The overall perspective of these articles was similar to the US-only authored articles, with 82.2% of the articles being judged favourable to the PBD hypothesis (Figure 7.5). There was a slightly greater rate of sceptical articles reflecting collaboration between US authors with sceptical perspectives on PBD (Carlson, Leibenluft, McClellan, Levin) with non-US sceptical authors (Duffy from Canada; James, Dubicka, Harrington from England; Werry from NZ; Parry from Australia). There was one consensus article (Goodwin GM et al. 2016) that promoted a traditional perspective. A slightly higher rate of SMD/DMDD articles reflects mostly the collaboration between Leibenluft in the US and Stringaris in England.

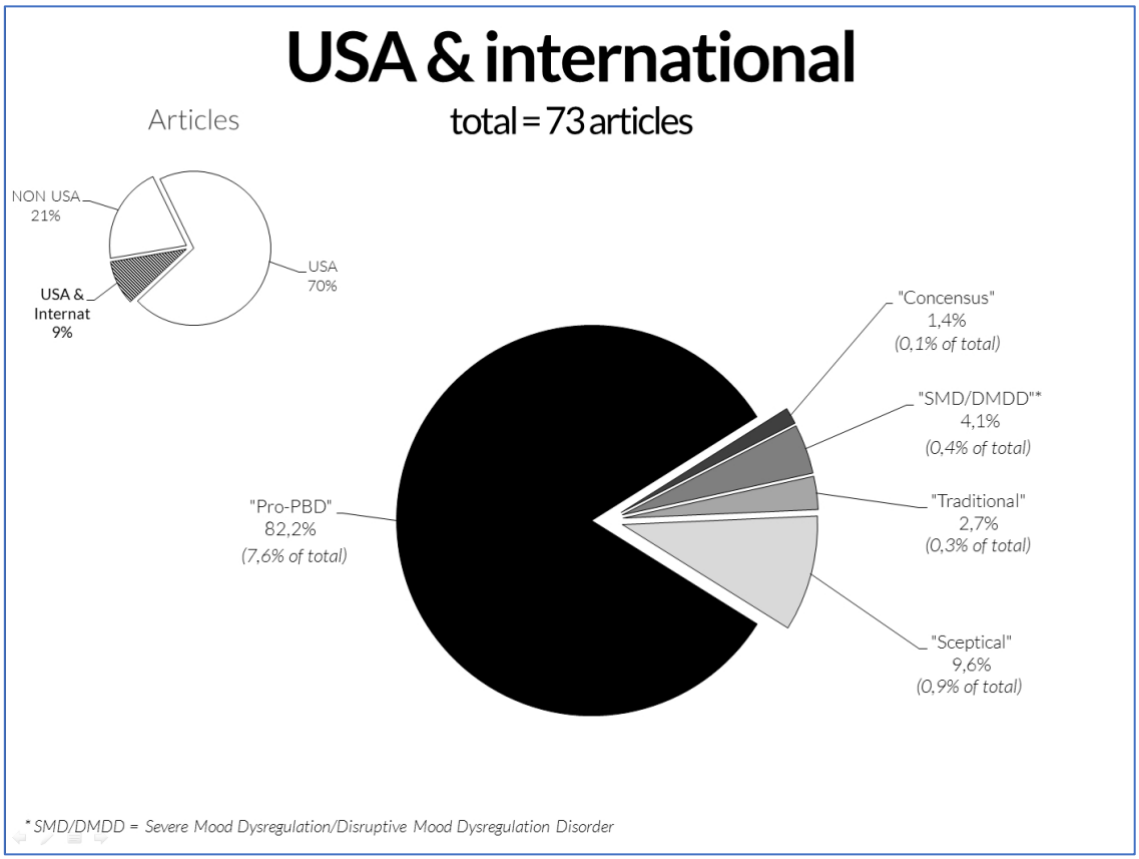


Figure 7.5: Breakdown of perspectives in articles with co-authors from US and non-US by institutional affiliation

7.3.3.3 **Perspectives of articles with authors from only non-US jurisdictions.**

For articles by authors outside of the US, in contrast to articles involving US authors, there was a greater rate of articles taking a traditional perspective (38.7%), or a sceptical perspective (18.5%) (Figure 7.6).

Taking into account that some articles were co-authored by authors from more than one non-US country, the numbers quoted here are higher than 162 in total (175 in fact). The traditional perspective articles (38.7%) were from: France, England (10), Canada, India (7), Germany (5), Netherlands, Switzerland (4), Denmark, Norway (3), Finland, Australia, Ireland, Spain, Sweden (2), and single articles from Austria, Belgium, Greece, Iran, Japan, Poland, Taiwan, Tunisia, and Turkey. The sceptical perspective articles were from: Canada (10), England (7), France (4), Australia (3), India, Sweden (2), and single articles from Germany, NZ and Wales.

Articles favourable to the PBD hypothesis amounted to 39.9% of the total and were from: Italy (12), Turkey (9), Brazil (8), Spain (7), Australia (6), Canada, France (5), India (4), Ireland (3), Germany, Mexico, South Africa (2), and single articles from Austria, England, Greece, NZ, South Korea and Sweden.

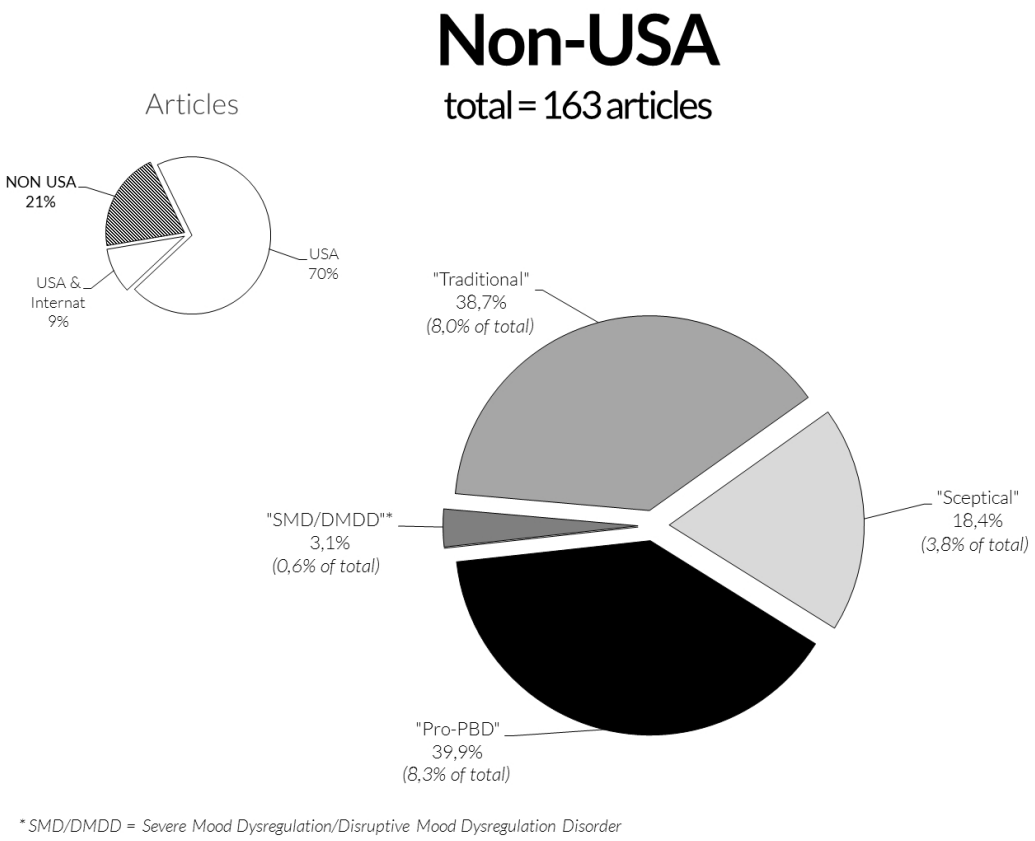


Figure 7.6: Breakdown of perspectives in articles by authors outside the US

7.3.3.4 **Further data analysis**

The citing articles from each of the 33 countries apart from the US were examined in more depth, dividing their articles into co-authored with US authors or not; this lengthy document can be requested from this author.

A table comparing countries according to numbers of pro-PBD versus sceptical/traditional articles comprises Appendix C5.

7.4 Discussion

7.4.1 Numerical dominance of US authors in the citation tree

The PBD literature has been dominated by articles from authors affiliated with US research centres (see Figure 7.1). The academic child psychiatric institutions with the most articles in this dataset are led by Biederman, Wozniak and colleagues from MGH-Harvard in Boston who continue to publish on 'broad-phenotype' PBD. The 'narrow-phenotype' PBD hypothesis originally from Geller and colleagues at WUSL, Missouri, has been taken forward with continuing research in the COBY study group of Birmaher, Axelson and colleagues at the University of Pittsburgh, Pennsylvania.

Within the citation tree an early article from the COBY group, titled "Clinical course of children and adolescents with bipolar spectrum disorders", published in *Archives of General Psychiatry* (Birmaher & Axelson 2006) had 351 citations by 25 July 2017. The COBY study article does appear to have gained proportionally slightly more international citations than the four seminal PBD articles chosen for this literature search (Figure 7.7), but many of these are Canadian and attributable to the work of Goldstein with affiliations in both Toronto and Pittsburgh.

Countries	n	% of 351
US	259	73.8%
Canada	58	16.5%
England	26	7.4%
Spain	18	5.1%
Brazil	14	4.0%
France	12	3.4%
Germany	12	3.4%
Italy	12	3.4%
Netherlands	6	1.7%
Norway	6	1.7%
Turkey	6	1.7%
Australia	5	1.4%
Hungary	4	1.1%
Mexico	4	1.1%

Czech Republic	3	0.9%
South Korea	3	0.9%
Sweden	3	0.9%
Switzerland	3	0.9%
Austria	2	0.6%
Ireland	2	0.6%
Wales	2	0.6%
Argentina	1	0.3%
Finland	1	0.3%
India	1	0.3%
Iran	1	0.3%
Lebanon	1	0.3%
Lithuania	1	0.3%
Nigeria	1	0.3%
Peoples R China	1	0.3%
Russia	1	0.3%
Taiwan	1	0.3%
Uruguay	1	0.3%

Figure 7.7: Citation tree showing breakdown of citations for Birmaher and Axelson (2006) by country, number, and percentage of total

The "Treatment guidelines for children and adolescents with bipolar disorder" article published in *JAACAP* (Kowatch et al. 2005; Chapter 4.8.2.7) was heavily cited as well: 262 times according to *Web of Science* as of 25 July 2017. The citation tree shows a similar geographic distribution to that for the four seminal articles (Figure 7.8). There was little change in the geographic distribution of citing articles for the last 5 years, suggesting the PBD hypothesis may not be gaining many new adherents internationally (Figure 7.9).

Countries	N	% of 245
US	197	80.4%
Canada	21	8.6%
England	9	3.7%
Netherlands	9	3.7%
Germany	8	3.3%
Spain	8	3.3%

Brazil	7	2.9%
Australia	5	2.0%
Italy	4	1.6%
Taiwan	4	1.6%
Austria	3	1.2%
France	3	1.2%
South Korea	2	0.8%
Switzerland	2	0.8%
Turkey	2	0.8%
Belgium	1	0.4%
Ireland	1	0.4%
Israel	1	0.4%
Japan	1	0.4%
New Zealand	1	0.4%
Wales	1	0.4%

Figure 7.8: Citation tree showing breakdown of citations for Kowatch et al. (2005) by country, number, and percentage of total

Countries	n	% of 60
US	46	76.7%
Canada	5	8.3%
Netherlands	4	6.7%
Spain	4	6.7%
Austria	3	5.0%
Brazil	3	5.0%
England	3	5.0%
Italy	2	3.3%
Taiwan	2	3.3%
Belgium	1	1.7%
France	1	1.7%
Israel	1	1.7%
South Korea	1	1.7%
Switzerland	1	1.7%

Figure 7.9: Citation tree showing breakdown of citations from the last 5 years only for Kowatch et al. (2005) by country, number and percentage of total

In 2016, a CME supplement with four (Kowatch, Findling, Fristad, Chang) of the authors from the 2005 treatment guidelines article, titled "Recognition and treatment of pediatric bipolar disorder", was published in the *Journal of Clinical Psychiatry.* The supplement had five articles titled: "Diagnosis, phenomenology, differential diagnosis, and comorbidity of pediatric bipolar disorder" (Kowatch 2016); "Evidence-based pharmacologic treatment of pediatric bipolar disorder" (Findling,2016); "Pediatric bipolar disorder: combination pharmacotherapy, adverse effects, and treatments of high-risk youth" (Chang 2016); "Evidence-based psychotherapies and nutritional interventions for children with bipolar spectrum disorders and their families" (Fristad 2016); "Evidence-based family interventions for adolescents and young adults with bipolar disorder" (Miklowitz 2016). Such a full supplement issue suggested PBD is still considered a fairly common diagnosis to make in US clinical practice and the articles still describe ultradian cycling and chronic irritability as core features of the PBD hypothesis.

7.4.1.1 **Role of US psychiatric journals in publishing the PBD literature**

The list in Figure 7.2 reveals 8 out of the 10 most frequently citing journals to be US based. As mentioned above, several journals have prominent US PBD researchers on their editorial boards. The paucity of articles in this dataset from major non-US child psychiatric journals is noteworthy. In contrast, for example, the journal of the European Society for Child and Adolescent Psychiatry (ESCAP), *European Child and Adolescent Psychiatry* had only 9 articles (Seymour et al. 2015; De Caluwe, Decuyper & De Clercq 2013; Halfon et al. 2013; Mikita & Stringaris 2013; Brunelle et al. 2009; Stringaris 2011; Consoli et al. 2007; Dubicka et al. 2008; Lazaro et al. 2007) out of the dataset of 787 citing articles. The two high-ranking journals of the UK based international Association for Child and Adolescent Mental Health (ACAMH), the *Journal of Child Psychology and Psychiatry* and *Child and Adolescent Mental Health*, had only four (Diaz-Caneja et al. 2014; Baroni et al. 2009; Stringaris et al. 2012; Gogtay et al. 2007) and two (Parry, Furber & Allison 2009a; Chan, Stringaris & Ford 2011) citing articles respectively. The perspectives of the 15 articles in these three journals were: pro-PBD 4; sceptical 3; traditional 2; SMD/DMDD 5. The four pro-PBD articles included one with all US authors, two with Spanish authors and one with French and Canadian authors.

This data adds further strength to the premise that the PBD hypothesis has remained mostly, but not solely, a US based diagnostic construct.

7.4.1.2 **Concentration of PBD research to several centres within the US**

Another noteworthy theme from this citation tree literature review was the concentration within the US particularly of pro-PBD articles, to the centres of MGH-Harvard; WUSL; University of Pittsburgh; the Ohio centres of University of Cincinnati, Case Western University and Ohio State University; UC San Diego, UCLA and Stanford University in California; University of Illinois in Chicago; and the University of North Carolina (Figure 7.1). Although a range of other US academic institutions had pro-PBD articles, several large institutions were conspicuous by their relative absence. This suggested, as conveyed to me anecdotally in my communication and visits with US child psychiatric colleagues (Chapter 4.8.2.21), that a large section of US child psychiatry, both clinical and academic, remained sceptical of the PBD hypothesis throughout the era of the PBD epidemic. Apart from Klein et al., Carlson and McClellan, it may have been that US sceptics struggled to get published.

7.4.2 **International articles in favour of the PBD hypothesis**

The 'citation tree' bibliometric analysis found several non-US academic child psychiatry centres that had embraced the PBD hypothesis and were conducting research on child and adolescent cohorts. These included the University of Pisa in Italy and recently extended to researchers from Rome, Latina and Perugia; University of Navarre and University of Barcelona in Spain; University of Sao Paolo and the University of Rio Grande do Sul in Porto Alegre in Brazil; University of Istanbul and University of Cukurova in Turkey; and a few articles also showing PBD research in South Korea and Mexico.

Most of these groups had collaborated with US researchers, in particular: the most published pro-PBD group outside the US, the University of Pisa, had co-authored six of their early articles with Akiskal (Dilsaver, Benazzi & Akiskal 2005; Masi et al. 2007; Masi et al. 2004; Masi et al. 2006; Masi et al. 2001; Masi et al. 2003); Soutullo and colleagues at the University of Navarre had co-authored with Biederman and colleagues (Soutullo et al. 2009; Escamilla et al. 2011) and also with DelBello (Soutullo et al. 2002); dual Brazilian and US affiliations of authors (University of Texas, University of North Carolina) characterised several pro-PBD articles,

though the research was primarily conducted in the US (Baloch et al. 2010; Olvera et al. 2004; Zappitelli et al. 2011); Diler, a Turkish-US national affiliated with the Pittsburgh group had co-authored with Turkish colleagues (Diler et al. 2007; Diler et al. 2008); and a recent South Korean study involved Youngstrom and Findling from the US (Lee et al. 2014). Professor Eric Youngstrom (University North Carolina) has been an adjunct professor at Korea University Seoul since 2009. Beyond these groups there was little worldwide research on PBD according to the analysis.

Regarding pro-PBD articles from Australia, France, India and the Netherlands, it appeared that some researchers in those nations explored the PBD hypothesis but ultimately concluded in retaining traditional perspectives. In Australia researchers in the state of New South Wales (University of New South Wales, Sydney University and Newcastle University) had several pro-PBD articles from the late 1990s to mid 2000s. However, a follow-up study of adolescent boys diagnosed with broad-phenotype PBD showed no progression to bipolar disorder in young adulthood (Hazell, P et al. 2003) and two authors who had seriously investigated the PBD hypothesis (P Hazell, 2013, email, 24 February; K Nunn, 2016, conversation, 2 October) confirmed that Australian researchers have concluded in favour of the traditional perspective.

Similarly, in France most of the pro-PBD articles were co-authored with US authors as part of the international BRIDGE Study Group (Chapter 1.2), or with US authors Findling or Akiskal, or Italian authors from the University of Pisa. Some of these articles concerned adult bipolar disorder but cited US PBD literature in a favourable manner. However, a recent article involving some of the same French authors appears to have taken a more traditional perspective, finding a stark difference in age at onset of bipolar disorder as established by retrospective recall in European compared with US adults (Bellivier et al. 2014). Other recent French articles have highlighted SMD/DMDD (Purper-Ouakil 2014; Purper-Ouakil, Vacher & Villemonteix 2014).

In the Netherlands sample, all 11 articles co-authored with US authors, mainly Post of the US NIMH and Faraone of MGH-Harvard, were judged to be pro-PBD, whereas the four Dutch articles without US authors were judged to take a traditional perspective. Willem Nolen, an emeritus professor at the University of Groningen and a past president of the ISBD, was co-author on many of these articles but also co-author to the Dutch offspring study separate to

the citation tree dataset that concluded: “Even after 12 years of follow-up, from adolescence into adulthood, Bipolar-I disorder was rare among offspring” (Mesman et al. 2013, p. 542).

In India, tertiary child psychiatric centres in their country have vast population catchments. as described to me by colleagues (S Basu, 2013, email, 1 August; M Sundaramugan, 2013, conversation, August; D Roy, 2015, conversation, September). Thus, more cases of rare neurodevelopmental disorders and early psychosis are seen proportionally in comparison to Western child psychiatric centres. Consequently, there was some initial interest in the PBD hypothesis, for example a cautiously favourable literature review of PBD (Reddy & Srinath 2000); however, a later study involving the same authors (Jaideep et al. 2006) examined the rate of ADHD, CD and ODD in ‘juvenile bipolar disorder’ and found low comorbidity in contrast to the US PBD literature. Most citing articles from India took a traditional perspective.

There was a single Mexican study (Palacios-Cruz et al. 2013) that used the K-SADS-PL to diagnosis a PBD cohort highly comorbid with disruptive behaviour disorders. Several literature reviews that presented the US PBD literature uncritically and accepting of the PBD hypothesis were mostly by individual authors from the Republic of Ireland (Carr 2009b; Carr 2009a), Greece (Fountoulakis 2010), South Africa (Scribante 2009; Bradfield 2010), Austria (Lackner et al. 2014) and Sweden (Skeppar & Adolfsson 2006).

7.4.3 Sceptical perspectives on PBD in the citing articles

Despite its proximity to the US, nearly all pro-PBD articles from Canada involved just one researcher, Professor Benjamin Goldstein (University of Toronto), who is affiliated with the COBY group from Pittsburgh. The CANMAT guidelines on bipolar disorder workgroup also cited the US PBD literature uncritically. Goldstein has since joined CANMAT along with Birmaher from Pittsburgh, and they appear to be the only two child and adolescent psychiatrists in a group of mainly Canadian adult biological psychiatrists. This limited number of child psychiatrists may explain the lack of scepticism from this distinguished organisation whose members include prominent research psychiatrists from across Canada.

This is particularly notable given that Canada had the most sceptical articles, due to the extensive work of Duffy and colleagues (University of Calgary; Canadian Institutes of Health Research and Dalhousie University; Chapter 4.8.7.1). Duffy has also co-authored with Carlson

who had the most US sceptical perspective articles. McClellan's critical commentary to the 2005 'treatment guidelines' in *JAACAP* was also in the data set of 787 articles. Carlson and McClellan were co-authors in two of the three 'consensus' articles in the US literature (McClellan et al. 2007; Carlson, Findling et al. 2009). These two 'consensus' articles were more an attempt than an achievement in consensus. They were remarkable for their strongly contradictory, sceptical and favourable perspectives on the PBD hypothesis within the articles (Chapter 4.8.2.12).

Another recently published, 'consensus' article (Goodwin, GM et al. 2016) had authors from seven countries including the US. Titled: "Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology", it contained a lengthy child and adolescent section. The overall theme was sceptical of both the 'narrow' and 'broad' PBD phenotypes, whilst emphasising vigilance for early-onset manic/hypomanic episodes. A quote from this section encapsulates this perspective:

> The diagnosis became controversial because 'childhood bipolar' diagnoses became increasingly common in some services in North America (Geller et al., 1995), but generally not in the rest of the world (Wals et al., 2001) … softening the diagnosis of bipolar disorder to allow irritability and chronicity risks confounding with more common problems such as ADHD and oppositional disorder … Affective instability is undoubtedly a component of what troubles many children, but it does not allow 'early diagnosis' of true bipolar disorder. (p. 513)

The two previous iterations of these British guidelines on treatment of bipolar disorder (Goodwin & Consensus Grp British Assoc, 2003; Goodwin & Consensus Grp British Assoc, 2009) also took sceptical perspectives on PBD. The data showed the UK has remained a bastion of scepticism towards the PBD hypothesis.

Elsewhere in Europe, this citation tree analysis suggests child psychiatry in Germany and Scandinavia, while less overtly sceptical in the tone of articles, has also maintained a solidly traditional perspective throughout the PBD era, consistent with the discharge diagnosis rate studies reported in Chapter 4.8.6.14.

7.4.4 Translation of academic literature to clinical practice

Given the synchronous rise in measurable clinical diagnostic rates of PBD with academic opinion, as expressed in the four key PBD articles, it seems apparent that the latter has been a significant factor in the increased rates of PBD diagnosis in the US. This has been accompanied by increased prescription rates of atypical antipsychotics and other medications for disruptive behaviour among US children and adolescents (Chapters 4.6.4; 4.8.4.2). In contrast, majority academic opinion in Canada, the UK, northern Europe, Australasia and India supporting the traditional/sceptical positions is likely to have minimised the uptake of PBD diagnosis and any subsequent increase in psychopharmacological treatment in clinical practice. Further, this citation tree literature review supports the clinical epidemiology (Chapter 4.8.6.14) that shows minimal spread of the PBD hypothesis particularly in the UK, northern Europe and Australia and NZ.

In contrast, this bibliometric analysis did find academic uptake of the PBD hypothesis in a few centres in Italy, Spain, Brazil, and Turkey. There were signs of PBD research in South Korea and Mexico and a smattering of review and opinion articles mainly by sole authors that were pro-PBD in orientation from Austria, Greece, Ireland, Sweden and South Africa. To what extent the academic pro-PBD perspective literature has translated into actual clinical practice in Italy, Spain, Brazil, Turkey and perhaps South Korea is yet to be clarified: so far, the published epidemiology and clinical opinion surveys of child psychiatrists on bipolar diagnoses in the paediatric age range have focused on the US, UK, Germany, Australia, NZ, Czech Republic, Denmark and Finland (Chapters 4.8.6.1; 4.8.6.11; 4.8.6.14) where the classical view has so far prevailed. Future research would benefit from the inclusion of studies in the southern Mediterranean and Latin American nations.

7.4.5 Limitations of this study

This citation tree analysis focused on the published academic debate that came after the publication of the two PBD source articles and the two *JAACAP* 10-year reviews first promoting the PBD phenotypes. As stated, this study did not attempt to cover the entire PBD literature: a larger body of PBD literature might reveal a more nuanced history of the academic debate. In any such future studies, the intensity of the PBD debate could be compared with the histories of other child psychiatric diagnoses such as ADHD, autism

spectrum disorder, and adolescent depression. Despite the limited scope of the current study, however, it provides an overview of the core of the international debate on PBD. Given the number of citations, it is probable that the larger PBD research groups have been identified by the current study.

A second limitation is the risk of bias in my being the sole arbiter of the 'preference' towards the PBD hypothesis of each article. I consciously applied the same standard to all articles, but it is possible that subconscious bias may have affected my decision making in US versus non-US studies. However, my reading of articles to discern which of the five categories to assign them was guided by my personal clinical and academic experience in child psychiatry and may have differed for others reading these articles. For that reason, a full list of the articles, most with abstracts attached and with preference categorisation applied, are available in Appendix C, so third-party assessment of the validity of choices can be made. An in-depth narrative analysis of all articles with at least one non-US author/co-author comprises Appendix C6.

7.5 **Conclusion**

This citation tree bibliometric analysis found that research on PBD had been widely published within the US but less so outside the US. Traditional perspectives on PBD predominated in non-US jurisdictions, including Canada, England, France, Germany and Scandinavia, and although groups had explored the PBD hypothesis in Australia, India and the Netherlands, the traditional perspective held sway. The exceptions to this were pro-PBD perspectives in academic child psychiatric centres in Italy, Brazil, Spain, Turkey and possibly South Korea. Co-authorship networks indicated such centres or neighbouring institutions in all those countries had collaborated directly with US PBD researchers. Further research is required on the translation of PBD into clinical practice in Italy, Brazil, Spain, Turkey and South Korea.

CHAPTER 8. LITERATURE REVIEW: ATTACHMENT & TRAUMA[3]

8.1 Introduction

8.1.1 Does the PBD literature consider attachment and trauma?

From the case of Esquirol's 8-year-old boy frightened by his nanny in the siege of Napoleonic Paris (Chapter 2.5.1), to media comments by professionals in the field such as van der Kolk from Harvard that the PBD diagnosis is given "with no understanding of the context of their life" (Carey 2007b, para. 22; Chapter 4.6.8), to the comments returned in our survey of the FCAP of the RANZCP (Appendix A7; Chapter 4.18.2), many common themes have emerged. This chapter concentrates on one of enormous significance: the neglect of contextual factors in children's lives, in particular those of attachment and developmental trauma. Quoting two of the respondents to the FCAP survey:

> "… From presentations I have attended at international conferences, the 'big names' in this area of research are not taking attachment issues into account when making a diagnosis." (Respondent 46, Appendix A7, p. 4)

> "[I]n my clinical experience, a number of children who have experienced early child abuse (in particular, sexual abuse in girls) and with complex or residual PTSD or PTS (Post Traumatic Symptoms) may lead to some inappropriate diagnoses of Bipolar Disorder or brief psychotic episodes." (Respondent 24, Appendix A7, p. 2)

It is a key hypothesis of this thesis that PBD arose during a time when psychiatry, particularly in the US, was in an era of biomedical reductionism. Attachment theory and developmental trauma are subjects of much research in psychology, sociology and related areas. However, many academic child and adolescent departments within the US have adopted a restrictive biomedical focus. Other possible reasons why the PBD literature appears to neglect such topics that are pertinent to disturbances of emotions and behaviour in childhood will be elaborated upon in the discussion section.

[3] *This chapter is largely similar to a published book chapter (Parry 2012f; Appendix A19).*

This chapter utilises a literature search that seeks to identify the quantity and quality of the coverage of contextual factors in the PBD literature that could explain or contribute to affective and behavioural dysregulation. Specifically, the PBD literature was searched for the terms: *attachment, child abuse, physical abuse, emotional abuse, sexual abuse, maltreatment, neglect, trauma* and *PTSD*. I presented some initial findings from this literature search as a poster at the Australasian Society for Bipolar Disorders (ASBD) conference in 2009 (Parry 2009a). The president of the ISBD at the time, Professor Michael Berk from Geelong, Australia, expressed a great deal of support for and interest in this issue, and later we collaborated on an article titled "Detached from attachment: neurobiology and phenomenology have a human face" (Dignam, Parry & Berk 2010; Appendix A12). In utilising psychiatric phenomenology and the neurobiology that mirrors it beneath the skull, there is always the risk that the researcher or clinician will reify symptom clusters with implied neurobiological causation. The risk then is neglect of the real-life contexts and subjective consciousness of patients' lives that may be contributing to such symptoms and neurobiological correlates.

8.1.2 Does the SMD/DMDD literature consider attachment and trauma?

As explored in Chapter 4.8.5 Leibenluft and colleagues redefined broad chronic irritable phenotype PBD as SMD, later defined as TDD and finally accepted into DSM-5 as DMDD. One of the stated aims in doing this was to reduce over-diagnosis of PBD. However, DMDD could easily become another childhood psychiatric diagnostic epidemic and some feared it would lead to similar problems of inaccurate reification and over-medicating (Frances 2010a). Thus, it is equally important to see whether contextual factors, particularly attachment and trauma, are considered in the SMD/TDD/DMDD literature.

8.1.3 Publication and presentation of these literature reviews

The initial poster presentation at the ASBD conference (Parry 2009a) was updated and presented at the IACAPAP 19th World Congress in Beijing (Parry 2010c). The data was further refined and presented at the 20th World Congress of IACAPAP in Paris (Parry 2012e). That same year also saw the publishing of an invited book chapter, "Paediatric bipolar disorder: are attachment and trauma factors considered?" in *Bipolar Disorder – Portrait of a Complex Mood Disorder* (Parry, 2012f; Appendix A19).

In 2013, I performed the same systematic literature review for presence or absence of attachment and developmental trauma factors in the SMD/TDD/DMDD literature. This body of literature was comprehensive and much smaller and more recent, the first articles appearing only in 2005. With this SMD/TDD/DMDD literature, I expanded my search terms to include parenting and family dynamic factors.

The rest of this chapter contains long passages from the book chapter (Parry, 2012f; Appendix A19).

8.2 Methodology

8.2.1 Defining a body of PBD literature

A body of PBD literature was defined by running a Scopus search in "Title-Abstract-Keyword" fields for [*pediatric* OR *paediatric* OR *juvenile* or *early-onset* OR *adolescen** OR *teenage** OR *child** OR *youth* OR *kids*] and [*bipolar* OR *mania* OR *manic* OR *hypomania* OR *hypomanic* OR *manic-depression* OR *manic-depressive*] for publications from 1995 to 15 June 2010. The search was limited to publications from 1995 when the described phenotypes of PBD appeared in the literature. This gave rise to 7,257 articles, although with low specificity for PBD articles. In Scopus an "All Fields" search detects a word in the article's list of references/citations as well as in title, keywords, and abstract. Within this body of 7,257 articles an "All Fields" search for the word 'attachment' found 165 articles of which 15 were PBD oriented articles. Full texts of these 15 articles were examined for context of use of the word "attachment".

In an email from the E-Helpdesk EMEA Coordinator at Elsevier who manage the Scopus search engine (B Zalac, 2013, email, 27 March), it was confirmed that an "All Fields" search detects a word in the fields below:

> I confirm that "search within results" indeed means "ALL FIELDS" search.
>
> "ALL FIELDS" stands for all the data within a Scopus article: *Abstract, Affiliation, Article number, Author, Collaboration Author, Chemical, CODEN, Conference Information, DOI, Editor, ISBN, ISSN, Issue, Keywords, Language, Manufacturer, Publisher, Publication Year, References,*

Sequence Bank, Sequence Bank Accession number, Source Title, Volume, and Article Title.

If you do not specify a field restriction, "ALL FIELDS" is assumed.

If you wish to search just for TITLE, ABSTRACT, KEYWORDS, REFERENCES, you can run this string search "TITLE-ABS-KEY(water) AND REF(water)"

To obtain a more specific body of PBD literature a Scopus search was conducted in "Title-Abstract-Keyword" fields for permutations of: [*pediatric* OR *paediatric* OR *juvenile* OR *youth* OR *child** OR *early* OR *adolescen** OR *teenage**] (with and without *"onset"* or *–onset*) and [*bipolar* OR *mania* OR *hypomania* OR *"manic depression"*] also [*bipolar* OR *manic* OR *hypomanic*] AND [*child** OR *teen** OR *"adolescen** OR *youth* OR *kids*] also [*bipolar* OR *mania* OR *hypomania* OR *"manic depression"*] AND ["*in a" – child* OR *boy* OR *girl* OR *adolescent*] also [*child* OR *boy* OR *girl* OR *adolescent* – "*with*"] AND [*bipolar* or *mania* or *hypomania* or *"manic depression"*].

As of 15 June 2010, the search found 1,223 publications. Perusal indicated high specificity to articles relating to PBD, which was rendered close to 100% by removing 110 articles concerned with purely classical perspectives of bipolar disorder in youth or adults with bipolar disorder.

This subset of PBD literature was then subjected to a Scopus "All Fields" search. To ascertain whether attachment theory and trauma aspects were considered, a search for the terms *attachment, trauma* (also detects posttraumatic/traumatized etc.) or *PTSD* or *maltreatment* or *abuse* was conducted.

8.2.2 **PBD literature affiliated with WUSL and MGH-Harvard researchers.**

The reality of time constraints precluded a manual search of all 1,113 articles in the PBD body of literature. However, two subsets of literature were defined by affiliation with the two academic child psychiatry departments that first promoted PBD: WUSL and MGH-Harvard. It was hypothesised that given the question of how much the PBD literature considered attachment theory and trauma factors, literature from institutions that had historically most influenced the PBD literature would give some important indication as to the question of

incorporation or otherwise of attachment theory and trauma concepts. In fact, there were 64 articles affiliated with WUSL, and 137 articles affiliated with MGH-Harvard. No articles were affiliated with authors from both institutions. Full texts of 198 publications were downloaded and manually searched for the terms: *attachment, trauma, PTSD*, *maltreatment*, *abuse*, and *neglect*. Three further articles were accessed by only abstract and citation list.

8.2.3 **Defining a body of SMD/TDD/DMDD literature**

To define a body of literature for DMDD and its two previous synonymous phrases, Scopus was searched in "Title-Abstract-Keywords" fields for *"severe mood dysregulation"* OR *"temper dysregulation disorder"* OR *"disruptive mood dysregulation disorder"* since 1999 until 19 March 2013. This search delivered 76 articles, the earliest dating from 2005. There were 69 English language (57 US, 3 UK, 3 Australia, 2 Canada, 2 German, 1 India, 1 Spain) and 7 non-English language (3 French, 1 German, 1 Czech, 1 Polish, 1 Hebrew) articles. I gathered all the articles in their full text format apart from the Hebrew article. The French, German, Czech and Polish articles had English abstracts.

Next, a full text search of all the English language articles, and a search of the English abstracts of the non-English articles, for the terms: *attachment, trauma, PTSD*, *maltreatment*, *abuse*, and *neglect* was performed. However, this time I also included *parent* (as in parenting) and *family* (as in family dynamics or therapy contexts).

8.2.4 **Defining a body of attachment theory literature**

A body of attachment theory related literature was defined by Scopus search in "Title-Abstract-Keywords" for [*"attachment theory"* or *"attachment security"* or *"attachment insecurity"* or *"avoidant attachment"* or *"secure attachment"* or *"insecure attachment"* or *"ambivalent attachment"* or *"disorganised attachment"* or *"reactive attachment"* or *"resistant attachment"* or *"attachment disorganisation"* or *"developmental psychology"* or *"developmental trauma disorder"* or *"developmental neurobiology"* or *"developmental psychopathology"* or *Bowlby*] resulting in 4,583 publications from 1995 to 13 June 2010. However, many did not have attachment theory as a major theme. To aid specificity the above terms were searched in "Title" field only, to give a sample of 746 publications.

This body of 'attachment theory related literature' was searched for the presence of PBD terms by searching within "All Fields" for [*"pediatric bipolar"* or *"pediatric onset bipolar"* or *"pediatric onset bipolar"* or *"paediatric bipolar"* or *"paediatric onset bipolar"* or *"juvenile bipolar"* or *"juvenile onset bipolar"* or *"early-onset bipolar"* or *"child* onset bipolar"* or *"child* bipolar"* or *"adolescen* bipolar"* or *"adolescen* onset bipolar"* or *teenage* bipolar"* or *"teenage* onset bipolar"* or *"pediatric mania"* or *"pediatric hypomania"* or *"paediatric mania"* or *"paediatric hypomania"* or *"juvenile mania"* or *"juvenile hypomania"* or *"early-onset mania"* or *"early-onset hypomania"* or *"child* mania"* or *"child hypomania"* or *"adolescen* mania"* or *"adolescen* hypomania"* or *"teenage* mania"* or *"teenage* hypomania"* or *"youth mania"* or *"youth hypomania"*]. Explicit terms such as these were used to define publications that specifically referred to PBD rather than publications dealing with attachment issues relating to offspring of adults with bipolar disorder. Only 8 articles were found.

8.3 Results

8.3.1 'Attachment', 'PTSD/trauma' and 'maltreatment/child abuse' in PBD literature

In 1,113 articles on PBD there were just 14 publications with the word 'attachment'; 29 publications with 'trauma/PTSD'; and 64 publications containing at least one of 'maltreatment/child abuse/sexual abuse/physical abuse/emotional abuse' in an "All Fields" (i.e. title, abstract, keywords, citation list) search. With overlap this amounted to 84 publications in total (Figure 8.1).

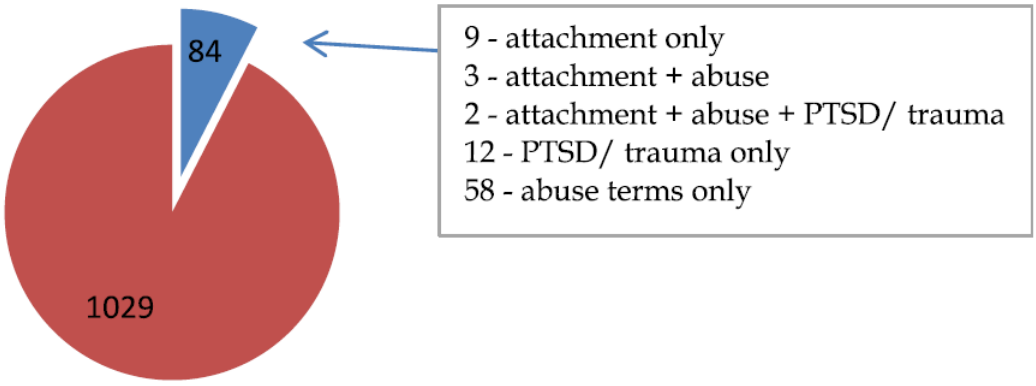


Figure 8.1: Attachment and maltreatment/trauma terms in PBD literature (Parry 2012f, p. 169)

8.3.2 **Fifteen PBD articles mentioning 'attachment'**

Fifteen PBD oriented articles from the less specific list of 7,257 articles contained the word 'attachment'. This included 10 of the 14 articles from the more specific list of 1,113 articles as 4 related to (non-PBD) offspring of bipolar parents' studies, plus a further 5 articles that were amongst the 7,257 articles. Thus 15 full-text articles were examined and the word 'attachment' was used in the following contexts:

8.3.2.1 **Attachment related concepts as a significant theme (3 articles).**

A case study (Bar-Haim et al. 2002) of a 7-year-old boy with multiple neurodevelopmental delays and diagnoses of PBD, ADHD and ODD included an attachment perspective. An article on family therapy for PBD children (Miklowitz, Biuckians & Richards 2006) accepted the validity of PBD phenotypes but promoted family therapy approaches: the word 'attachment' was only mentioned in one citation title in the references list. A review of PBD (Carlson & Meyer 2006; Chapter 4.8.3.2) was critical of over-diagnosis of PBD, noting that PBD research "would benefit from a developmental psychopathology perspective" (p. 939), and history taking should include "quality of attachment relationships, abuse history … as well as relevant family factors" (p. 940).

8.3.2.2 **Attachment in text as minor theme (5 articles)**

An AACAP research forum on early-onset bipolar disorder (Carlson, Findling, et al. 2009) contained a passage on contextual issues, maltreatment and family dysfunction. The research forum article mentioned "insecure attachment" as a "risk factor for emotional dysregulation and externalizing disorders" among offspring of parents with bipolar disorder (p. 7). This was one of the very few documents to use the terms "maltreatment" and "insecure-attachment", although there was no specific mention of neglect or PTSD (p. 7).

Dickstein and Leibenluft (2006) reviewed differences between 'narrow phenotype' PBD and 'severe mood dysregulation', including neuroimaging differences and referred to attachment theory based neurobiology research. The article mentions concepts from the attachment theory-based literature, for example, the importance of facial gaze in mother-infant dyads "to foster attachment between infant and caregiver" (p. 1113,) and highlighted the importance of the amygdala in recognising the emotions of others.

A personal perspective on a career in child psychiatry (Cytryn 2003) noted "insecure attachment" was found in a small prospective study of offspring of mothers with bipolar disorder (p. 7). The offspring developed psychiatric disorders but not PBD, however, the article was supportive of the concept of PBD. McClure et al. (McClure, Kubiszyn & Kaslow 2002) expressed caution about the validity of PBD diagnoses and noted attachment perspectives must be fully covered in history taking and observations of child-family interactions. Parens and Johnston (Parens & Johnston 2010) summarized an interdisciplinary workshop titled "Controversies concerning the diagnosis and treatment of bipolar disorder in children". 'Attachment' is in a citation title, and mentioned once in the text:

> [W]orkshop participant and child psychiatrist Mary Burke speculated that, in the underprivileged community where she practices, one of the most effective ways to help children now receiving the BP diagnosis would be to promote attachment and reduce stress on families. (p. 3)

Although, attachment is mentioned in all these articles so far, none had expanded on the full relevance of the term, nor was there any direct research involving instruments that measure attachment amongst PBD cohorts. The following articles had even less on this bedrock concept in developmental psychology and psychopathology.

8.3.2.3 **'Attachment' only in a citation title (5 articles)**

A review (Post & Leverich 2006) of psychosocial stress as a risk factor for earlier onset and exacerbated course of bipolar disorder discussed the ameliorating influences of psychotherapy and psychoeducation. 'Attachment' was mentioned in the title of a reference (Insel 1997) which was used in an in-text description of animal attachment-oriented studies, noting that these studies "should make one extremely cautious in ascribing what appear to be genetic predispositions to genes, as opposed to familial/environmental influences that can themselves determine lasting neurobiological and behavioral traits" (p. 1184).

In a study (Meyer, SE et al. 2006) of the Wisconsin Card Sorting Test in adolescent offspring of mothers with bipolar disorder, 'attachment' was mentioned in the title of a reference (Cicchetti, Toth & Rogosch 1999) for the passage:

> Our results suggest that early exposure to extreme levels of maternal negativity appears to increase the risk for apparent frontal lobe dysfunction, which in turn, heightens vulnerability for the development of bipolar illness. This suggests that prevention efforts with high-risk families should go beyond children's symptomatology to focus on ways of improving the environments in which they are developing. (p. 586)

An article (Costello et al. 2002) that discussed abuse and parenting as minor themes had 'attachment' in a citation title (Nachmias et al. 1996) which was used as a reference for: "evidence suggests that responsive caretakers may buffer the risk for depression and other forms of psychopathology" (p. 533). *Another (Hirshfeld-Becker et al., 2003) had* 'attachment' in a citation title (Manassis et al. 1995), which was referenced along with others to say "some studies find an association between behavioral inhibition and anxiety disorders" (p. 987), and a fifth (Petti et al. 2004) had 'attachment' in a citation title (Greenberg, MT, Siegel & Leitch 1983) which was referenced in relation to a life events checklist that did not address attachment concepts, although social relationships were discussed.

8.3.2.4 **"Parent-child relationship" as keyword synonym for "attachment" (1 article):**

The keyword "parent-child relationship", not "attachment", appears to have led Scopus to choose an article (Schenkel et al. 2008) when searching for "attachment". The article stated that "compared to controls, parent–child relationships in the PBD group were characterized by significantly less warmth, affection, and intimacy, and more quarrelling and forceful punishment" (p. 422).

8.3.2.5 **"Reactive Attachment Disorder" (1 article).**

One article (Marchand, Wirth & Simon 2005) did not refer to attachment theory, but to "Reactive Attachment Disorder" in the DSM-IV sense. However, the article focused on trauma and complex PTSD as differential diagnoses to PBD, noting: "children with symptoms suggestive of bipolar disorder must be carefully screened for exposure to adverse events" (p. 74).

8.3.3 Full text searches of two prominent PBD research academic centres

The above search for attachment, trauma and maltreatment terms was in "all fields" so it would not have detected terms if they were in an article's text but not in the title, abstract, keywords or citations. One-hundred and ninety-eight articles from authors affiliated with WUSL and MGH-Harvard were full text searched. Three articles (1 from WUSL, 2 from MGH-Harvard) were only accessed by abstract and citation lists and none of the searched terms were found. Of the 201 total articles, 64 were affiliated with the WUSL group and 137 with the MGH-Harvard group.

8.3.3.1 PBD literature affiliated with WUSL

With overlap, 11 of 64 articles contained at least one of the searched terms except for 'maltreatment' (Figure 8.2).

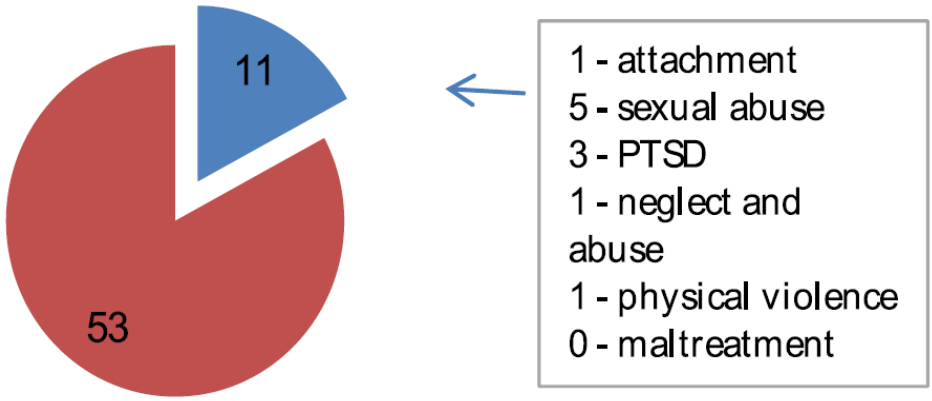


Figure 8.2: Attachment and maltreatment/trauma terms in WUSL PBD literature (Parry 2012f, p. 171)

As previously mentioned, one article (Costello et al. 2002) contained 'attachment' in a citation title. However, though discussing the child subjects' social and family relationships, the article did not address 'attachment' per se in the text.

Five articles (Geller & Luby 1997; Geller et al. 2000; Geller, Zimerman, Williams, DelBello, Bolhofner, et al. 2002; Craney & Geller 2003; Geller et al. 2005) contained the term 'sexual abuse'. These referred to 'sexual abuse' as a differential diagnosis for 'manic hypersexuality', but concluded that as only 1.1% of the cohort of 93 children with PEA-BP (pre-pubertal and early-adolescent-onset bipolar disorder) could be diagnosed with 'sexual abuse or

overstimulation', whereas 43% (particularly the children who had hit puberty) had 'manic hypersexuality', leading Geller to suggest this "strongly supports hypersexuality as a symptom of mania" (Geller, Zimerman, Williams, DelBello, Bolhofner, et al. 2002, p. 23).

PTSD was mentioned (Geller et al. 2004) in a list of potential differential or comorbid diagnoses for the cohort of 93 (86 at follow-up), noting no cases of PEA-BP had PTSD. Another article (Geller et al. 2009) also mentions zero cases of PTSD in a diagnostic list for forty-seven 14-year-old PBD subjects in a neuroimaging study. A further article (Luby & Navsaria 2010) had PTSD in a citation title but PTSD/trauma was not mentioned in the text.

The terms 'physical violence' and 'sexual abuse' were listed in a 'Life Events Checklist' and it was noted that with the cohort of 93 PEA-BP children there were significantly more adverse life events checked than for both ADHD and normal control groups (Tillman et al. 2003). The authors concluded:

> Because there was no a priori reason to expect significantly more independent life events in the PEA-BP compared to the ADHD and NC groups, these results warrant further research into the role of life events in the onset of PEA-BP. (p. 243)

A study (Luby & Belden 2008), of 21 Bipolar-I depressed preschoolers compared with 54 unipolar depressed preschoolers as diagnosed by the PAPA (Preschool Age Psychiatric Assessment that is based on DSM-IV), mentioned 'neglect' and 'abuse' in the following context: "adverse environmental outcomes include neglect and/or abuse as well as psychosocial stressors and trauma" (p. 1963). They concluded:

> … the finding that preschoolers with this bipolar syndrome did not experience greater trauma or adverse life events than other groups is also of importance. While this does not confirm the syndrome is a bipolar disorder, it does suggest that it cannot be explained by developmental deviation secondary to trauma, as has been widely speculated. However, longitudinal follow-up data will be needed to more definitively clarify this nosologic issue. (p. 1967)

The authors did note a limitation of the study, that "Findings are also limited by sole reliance on parent report of symptom states, frequencies and duration." (p. 1968)

One article (Craney & Geller 2003) didn't mention attachment theory by name but did note that 2-year follow-up research with the PEA-BP cohort of 93 children found "low maternal warmth" the only predictive factor for relapse of mania. The risk was strong: "Subjects with low maternal–child warmth were 4.1 (95% CI ¼ 1.7–10.1) times more likely to relapse after recovery (19). No other baseline characteristics (e.g. MDD, CGAS, mixed mania, continuous cycling, psychosis, ODD/CD) predicted recovery or relapse." (p. 253)

In fact, there was a 100% relapse over 2-year follow-up for those with low maternal warmth compared with 40% relapse for those with high maternal warmth. They concluded that this was a similar effect to high expressed emotion (EE) in schizophrenia, and that "these data from the PEA-BP sample strongly point toward the need for research on non-pharmacological modalities." (p. 255)

8.3.3.2 **PBD literature affiliated with MGH-Harvard**

Of 137 articles affiliated with MGH-Harvard, 23 articles contained at least one of the searched-for terms somewhere in the full text and reference list (Figure 8.3).

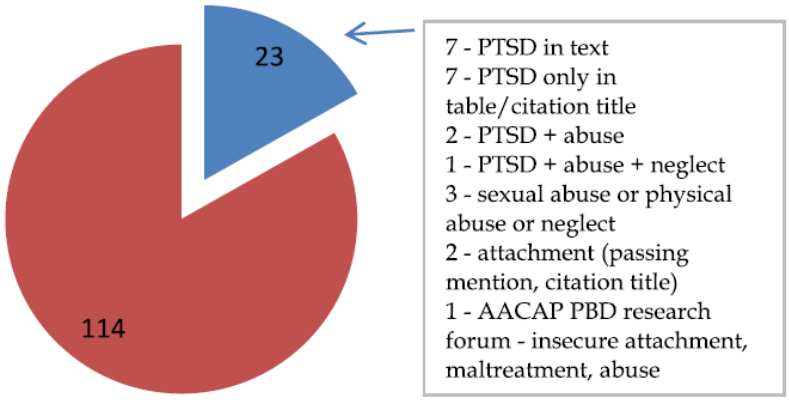


Figure 8.3: PBD literature affiliated with MGH/Harvard (Parry 2012f, p. 173)

The word 'attachment' appears in 2 articles. Henin et al. (2005) mentioned 'attachments in infancy' in the passage:

> The few studies that have examined the psychosocial functioning of children at risk for mood disorders have suggested that these children display poorer social skills and attachments in infancy (Zahn-Waxler et al. 1984), as well as deviant school behaviors (Weintraub et al. 1975, 1978), impaired academic performance

> (McDonough-Ryan et al. 2000, 2002), suicidality (Klimes-Dougan et al. 1999), and poorer peer social networks (Pellegrini et al. 1986) in childhood. Taken together, these findings suggest that bipolar disorder may be characterized by extensive premorbid social and academic maladjustment. (p. 559)

Biederman et al. in 1998 (Biederman et al. 1998) mentioned 'reactive attachment disorder' in a passage:

> [A] key limitation of our work: neither the structured interview diagnoses nor the clinical chart ratings can be accepted as unequivocal evidence for the diagnosis of bipolar disorder. For example, some of our patients met criteria for PTSD, and we did not assess for other disorders such as reactive attachment disorders that might present with manic symptoms. Thus, although our results demonstrate a link between mood stabilizer treatment and manic-like symptoms, they are not definitive as regards the treatment of bipolarity. (p. 635)

Neither paper elaborates upon attachment theory beyond those statements. Also, the statement from Biederman et al. (1998) is somewhat at odds with the reported findings in the 16 other articles that mention PTSD. Nine of these articles (Spencer, Biederman & Wilens 1999; Hirshfeld-Becker et al. 2006; Wilens et al. 2003; Wilens et al. 2008; Moore, Biederman, et al. 2007; Moore, Frazier, et al. 2007; Frazier et al. 2007; Harpold et al. 2005; Joshi & Wilens 2009) only mentioned PTSD as follows:

- In a diagnostic list of anxiety disorders (Spencer, Biederman & Wilens 1999; Hirshfeld-Becker et al. 2006).
- As a comorbid diagnosis with 14% of preschool and 10% of under-age-10 PBD diagnosed children (Wilens et al. 2008).
- As one comorbid PTSD case in a cohort of 18 PBD diagnosed children (Moore, Biederman, et al., 2007) and two of 32 PBD diagnosed children (Moore, Frazier, et al. 2007) and another article on the same cohort listed two of 28 PBD diagnosed children comorbid for PTSD (Frazier et al. 2007).
- As one of all anxiety disorders that occurred with high rates in a PBD cohort, of which PTSD had the highest odds ratio of correlating with PBD (Harpold et al., 2005). The authors concluded "our results indicate that BPD (bipolar disorder) significantly and robustly increased the risk of a broad range of anxiety disorders in youth" (p. 25).

- As having high comorbidity rates with PBD in a table, in another study (Joshi & Wilens 2009).

Wozniak (2003) did refer to PTSD in the text of her article, noting that PBD research has been criticized amongst other things for "difficulty in distinguishing bipolar disorder (BD) from other conditions marked by irritability such as attention deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder (PTSD)" (p. 938).

Three papers that dealt with the issue of trauma and PTSD more directly in the text concluded that PBD precedes trauma and PTSD, suggesting that a child with PBD is so disruptive that they create traumatic situations and family relationships that then impact traumatically upon them. Biederman et al. (2000) and Biederman et al. (2003) both refer to an earlier Wozniak et al. (1999) study. Both Biederman et al. articles contain the same passage that states:

> Using data from a longitudinal sample of boys with and without ADHD, Wozniak et al. (1999) identified paediatric bipolar disorder as an important antecedent for, rather than consequence of, traumatic life events … When traumatized children present with severe irritability and mood lability, there may be a tendency by clinicians to attribute these symptoms to having experienced a trauma. To the contrary, longitudinal research suggests the opposite: mania may be an antecedent risk factor for later trauma and not represent a reaction to the trauma (Wozniak et al. 1999). (Biederman et al. 2000, p. 463; Biederman et al. 2003, p. 296).

In a departure from conventional theories of early childhood development and the interaction of child abuse with children's emotional and behavioural dysregulation, Wozniak et al. (1999) had indeed reported:

> Our results showed that the diagnosis of bipolar disorder at baseline assessment in children with ADHD was the most significant predictor of the development of later trauma during the 4-year follow-up period. Although not entirely surprising, this finding, to our knowledge, has not been previously reported. Considering that mania is a very severe disorder with high rates of explosiveness, aggression, impulsivity, and poor judgement (Wozniak et al. 1995a), it could predispose an affected child to trauma exposure. (p. 53)

The range of traumatic experiences considered were typical, trauma was defined as:

> An event outside the normal range of human experience … included violence, any physical or sexual abuse, rape, any life-threatening experience, and witnessing or experiencing a terribly frightening event in which they or another person were in danger of being killed or badly hurt. (p. 50)

Basing their data on parental questionnaires of the sequence of events, Wozniak et al. (1999) concluded:

> If confirmed, these results could help dispel the commonly held notion that mania-like symptoms in youths represent a reaction to trauma. (p. 54)

The Wozniak et al. study was a 4-year follow-up study of 128 boys with ADHD (of whom 14 were diagnosed on structured interview with comorbid PBD at baseline and a further 7 diagnosed with PBD at the 4-year follow-up) plus 109 normal controls of whom 2 were diagnosed with comorbid PBD at follow-up. Fifteen of the 128 experienced a traumatic event and 4 (27%) of these 15 had comorbid PBD compared to 10 (9%) rate of comorbid PBD in the 113 ADHD boys without traumatic events during the follow-up period. The authors noted limitations:

> [O]ur number of trauma-exposed subjects (including controls) was relatively small (n=23), and a very small number of traumatized subjects (n=2) went on to develop PTSD … our results should be viewed as preliminary until confirmed with larger samples. (p. 54)

They also noted they did not assess for PTSD at baseline:

> [T]he findings reported in this study must be seen in light of methodological limitations. Since we assessed trauma only for the 4-year follow-up period and did not make a lifetime assessment of trauma, we cannot rule out the possibility that trauma could have predated or contributed to the development of bipolar disorder in some children. However, if trauma were to lead to mania rather than the other way around, we should have found that children without mania traumatized during the follow-up period would be more likely to go on to develop mania. This was not the case in our study. (p. 54)

Additionally, whilst the study reported 1 child (out of 237) had experienced “physical abuse” and 3 children experienced “sexual abuse”, the study does not report on any verbal or emotional abuse in the “types of trauma” examined (p. 51).

The ages of the boys at the 4-year follow-up were peripubertal on average (ADHD 10.3, SD 2.9; ADHD + Trauma 12.3, SD 3.1; Control 11.5, SD 3.6; Control + Trauma 12.0, SD 4.1) and it is not reported as to what extent early life attachment factors were assessed (p. 50). Wozniak et al. (1999) stated:

> The literature suggests that protective factors operating at various stages of development may buffer children from posttraumatic suffering. For example, in a study of children and adults surviving SCUD missile attacks in Israel, symptoms in children correlated with symptoms in their mothers. These authors concluded that maternal stress-buffering capacity plays a crucial role in minimizing suffering in traumatized preschool children (Lahor et al. 1997). (p. 52)

Despite this passage Wozniak et al. do not appear to elaborate on parent-child relationships as mediating stress in their study. Also, only parents and not children were interviewed if the child was under age 12, therefore presumably most children were not interviewed at baseline.

A more recent article (Steinbuchel et al. 2009) affiliated with MGH-Harvard found an increased rate of PTSD in adolescents with PBD, though also tending to view PBD as a risk factor for PTSD. Subjects with both PTSD and PBD developed significantly more substance use disorders (SUD) and the authors concluded that “follow-up studies need to be conducted to elucidate the course and causal relationship of BPD, PTSD and SUD” (p. 198). Another article (Althoff et al. 2005) was also cautious in tone, stating:

> In 2005 the idea is clearly not ‘nature v nurture’ but ‘nature and nurture and how they interact’. Recent discoveries have shown the interaction between the serotonin transporter gene and trauma affecting likelihood of MDD and reduced by presence of positive social support. Thus far there have not been studies of specific G X E interactions with JBD. (p. 605)

Further caution was expressed in a study (Faraone, Biederman & Monuteaux 2001) of girls with ADHD and bipolarity, who commented that "We did not assess for post-traumatic stress disorder (PTSD), which often is expressed with symptoms of ADHD and bipolarity. Thus, we cannot determine if cases of PTSD may have obscured our results (p. 25)."

A recent article (Doyle et al. 2010) reported on a lack of specificity in the Child Behaviour Checklist (CBCL) for diagnosing JBD (Juvenile Bipolar Disorder, used synonymously with PBD):

> The items on the three scales that contribute to the CBCL-JBD profile reflect emotional and behavioral lability and distractability, i.e., items that index the capacity for self-regulation across a wide range of domains (i.e., cognitive, behavioral and affective). Further evidence for this conceptualization comes from Ayer et al. who found that the CBCL–JBD phenotype can be modeled as sharing a single latent trait with a different secondary CBCL scale purported to measure post-traumatic stress problems (PTSP). Like the CBCL-JBD phenotype, the PTSP scale is associated with suicidality and poor outcome and features a number of items overlapping with the CBCL-JBD that relate to self-regulation. Based on this analysis, the authors suggest both scales index a single dysregulatory syndrome. The fact that the CBCL-JBD phenotype taps into a trait relevant to a range of psychiatric disorders may help to explain the profile's lack of diagnostic specificity to juvenile-onset BPD in clinical studies. (p. 383)

Six articles mentioned the term 'abuse': physical and sexual abuse were listed in a trauma list (Wozniak et al. 1999); passing mention was made to sexual abuse as a differential to manic hypersexuality (Soutullo et al. 2009); physical and sexual abuse were briefly mentioned in relation to PTSD (Steinbuchel et al. 2009); abuse occurred in a citation title which is referenced in the text: "findings in the pediatric (Ackerman et al. 1998) and adult (Kessler et al. 1995) literature document high rates of comorbid PTSD in bipolar subjects" (Harpold et al. 2005, p. 24); a study (Faedda et al. 2004) reported "no history of physical or sexual abuse was found in any case" in a cohort of 82 PBD children (73% pre-pubertal with 74% having "onset of first symptoms" under age 3) (p. 308).

Another article (Bostic et al. 1997) mentioned infants being depressed in "neglectful or abusive situations" (p. 1489). Otherwise 'neglect' is not mentioned by MGH-Harvard authors except in the context of 'neglect of PBD' as a diagnosis. The term 'maltreatment' is not

mentioned. However, the AACAP 2006 Research Forum (Carlson, Findling, et al. 2009) had co-authors from the MGH-Harvard group and as above did mention maltreatment and abuse specifically.

8.3.4 PBD terms in the attachment theory literature

As shown in Figure 8.4 terms relating to PBD were conspicuously absent.

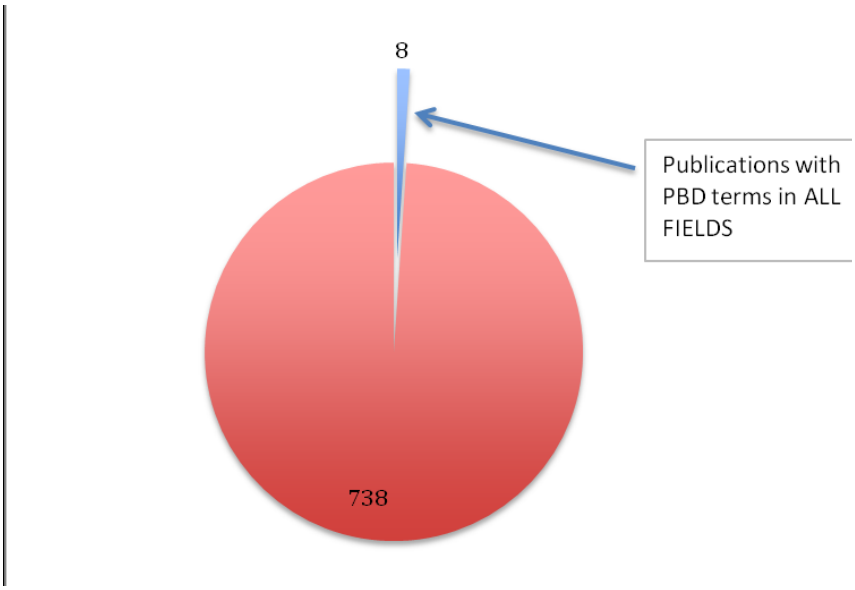


Figure 8.4: Proportion of attachment theory literature containing PBD terms

Just 8 papers were found by Scopus search for PBD terms in "All Fields" from a body of 746 attachment and trauma articles. However, on close examination not all these articles were strong on attachment-theory-based themes. The main focus for seven of these was on anxiety and depression arising out of parent-child relationships. PBD was only a major theme in a single article, an editorial (Miklowitz & Cicchetti 2006) about a journal issue devoted to PBD. This was therefore more an article in the PBD literature than in the attachment-theory-based literature. It possibly was selected by Scopus as attachment-oriented because of the phrase 'developmental psychopathology' in the title and text. 'Sexual abuse' is in the title of a reference. The editorial doesn't contain the word 'attachment' nor 'PTSD/trauma' nor 'maltreatment'. Therefore, the results reveal that this sample of attachment-theory-based literature does not seriously consider the PBD hypothesis.

8.3.5 A comparison of neuroimaging reviews from PBD literature and attachment/trauma literature

Allan Schore (associate professor of psychology at UCLA) is a prominent author in the attachment and developmental trauma literature who has reviewed neuroimaging research data in two books (Schore 2003a; Schore 2003b) and a review article (Schore 2002). The indexes of each book do not contain the word 'bipolar', and 'mania' is mentioned only once in each book, in reference to right orbitoprefrontal cortex (ROPFC) dysfunction, though the majority of each book focuses on the ROPFC causing more general affect dysregulation leading to other disorders and describes how this dysfunction arises in disorders of attachment and trauma. The terms "bipolar", "mania/manic" or "hypomania/hypomanic" do not occur in the review article.

Pavuluri et al. (2009) reviewed neuroimaging studies in PBD. None of the terms for attachment, PTSD or maltreatment or abuse appear. Yet strikingly both Schore's and Pavuluri's reviews describe very similar findings concerning the right pre-frontal cortex and limbic system, including right amygdala reactivity.

8.3.6 Attachment and trauma terms in the SMD/TDD/DMDD literature

Of the 69 English language articles, 40 contained none of the search terms anywhere within the articles. The following findings are from the remaining 19 articles.

8.3.6.1 "Attachment" in the SMD/TDD/DMDD literature (3 articles)

The report of the two-day workshop discussing PBD referred to previously (Chapter 4.8.2.23) (Parens & Johnston 2010) was an article found in both the PBD literature sample and the SMD/TDD/DMMD sample, and contained the passage mentioned in the above section, i.e.: "Mary Burke speculated … effective ways to help children now receiving the BP diagnosis would be to promote attachment" (p. 3).

An Australian article (Jairam, Prabhuswamy & Dullur 2012) from the Sydney based group of PBD researchers contained the following passages referring to individuals diagnosed with PBD/SMD:

> They usually have very poor emotional regulation with significant outbursts, poor frustration tolerance, insecure attachments, and a learned pattern that temper tantrums and threats succeed in getting them what they want.
>
> Both family-focused therapy and multifamily psycho-education appear to show promise. This area needs particular attention as medication alone is unlikely to be successful ... Other factors to consider… [include] … comorbid psychiatric disorders, attachment difficulties, and family dysfunction. (p. 6)

Another Australian article by Melissa Raven and myself from Flinders University (Raven & Parry 2012; Appendix A24) was captured by the Scopus search, as we had referred to PBD and DMDD in a discourse about the pharmaceutical industry's use of DSM labels:

> (Pharmaceutical company) economic[s] might … [give] … the 'pill-for-every-ill' model greater sway in the minds of patients, clinicians, researchers, and health regulators. By comparison, alternative theoretical perspectives, such as evolutionary psychology, psychodynamic theory, and attachment theory, and different contextual perspectives – trauma oriented, family systemic, social, cultural, and economic – receive far less attention. (p. 512)

8.3.6.2 **"Trauma/PTSD" in the SMD/TDD/DMDD literature (10 articles)**

Five articles listed the DSM-5 criteria for DMDD and simply included the fact PTSD is an exclusion criterion without any further elaboration.

Four other articles made only a brief passing mention of PTSD, firstly:

> The few studies that investigated startle response in children found greater fear-potentiated startle in children with negative affect[28] and PTSD[29], but decreased startle in children with disruptive behavior disorder[30], when compared with controls." (Rich et al. 2005, p. 538)

Secondly, PTSD is included in a diagnostic list (of 2 out of 14 subjects) without further elaboration (Rau et al. 2008); next, in the title of a citation without elaboration in the text of the article (Adleman et al. 2011); and finally, in passing mention unrelated to SMD/TDD/DMDD (Calles 2011).

An Australian author in an opinion article in *Psychiatric Times* (McLaren 2011) critiqued decontextualized psychiatric nosology in the current DSM model and suggested: "Early trauma complicates adult affective disorder by predisposing to substance abuse, criminality and personality disorder" (p. 2).

8.3.6.3 **"Abuse" and "maltreatment" in the SMD/TDD/DMDD literature (5 articles)**

Two articles mentioned 'abuse' briefly. Rich et al. (2008) made passing mention of 'abuse' in a list of 'childhood psychopathologies' with regards to "processing facial emotions" (p. 541); 'abuse' was also in 3 citation titles. Baroni et al. (2009) stated that "youth can provide important information about … hallucinations or delusions, and about abuse they may have suffered" (p. 209).

Three other articles made strong points about the need to be aware of child abuse. Carlson, Potegal et al. (2009) in a study of children with 'rages', found: "Fifty-six children (43%) [with rages] were known to have been exposed to significant violence, including physical and/or sexual abuse" (p. 283).

Axelson (2013) emphasised that it is "… imperative for clinicians to search for potential causes of severe irritability … psychosocial stressors, history of maltreatment, family conflict ..." (p. 138).

Finally, a British article (Taylor 2009) elaborated on the sequelae of abuse and noted how the symptoms of 'irritability' and hypersexuality lack diagnostic specificity. He was referring to PBD as well as SMD/TDD:

> [Irritability] simply means the child is very easily provoked to anger and it can be … [a] sequelae of physical abuse.
>
> Hypersexuality can arise for reasons other than bipolar disorder, especially if the young person has been sexually abused, but it can also lead professionals to suspect abuse when the true reason is an altered mood state. (p. 486)

8.3.6.4 **"Parenting" in the SMD/TDD/DMDD literature (5 articles)**

Science journalist Miller (2010) wrote about PBD and SMD/TDD in terms of the controversies and the proposed (at that time) new diagnosis of TDD for DSM-5 to combat the over-diagnosis

of PBD. The term 'parenting' featured in the following context. The author was interviewing Susan Resko, the director of the CABF:

> The word 'temper' in the name of the disorder reminds some parents of the days when doctors blamed childhood behavioral problems on bad parenting, Resko says: 'It conjures images of inept mothers who cannot control their bratty kids.' Her group is lobbying for 'mood' or 'affect' to be used instead. (p. 1193)

Taylor (2009) from the UK who had made the above points about irritability and hypersexuality possibly being sequelae of physical and sexual abuse, also made brief mention of parenting in terms of parent training interventions, suggesting that "… If mood dysregulation persists … parent training can be considered, as outlined in a Cochrane review …" (p. 489).

This point was echoed by Stringaris, in an article published in *European Child and Adolescent Psychiatry* (Stringaris 2011). He commented that: "it may well be that the effects of irritability can change dramatically through environmental modification (e.g. following parenting interventions) ..." (p. 65).

Another article made brief passing mention of parent-training but did not elaborate (Waxmonsky et al. 2008) in noting: "Parents attended a weekly parent-training course …" (p. 577).

Batstra, a Dutch author, and colleagues that included Allen Frances (Batstra et al. 2012) published: "Childhood emotional and behavioral problems: reducing over-diagnosis without risking under-treatment" that was captured by the Scopus search for SMD/TDD/DMDD. They used the word 'parent' in the following contexts:

> [A] diagnostic label can lead to negative parental and teacher expectations, which may be perceived by the child who in response may underperform (Pygmalion effect). (p. 493)

> [S]ocietal factors (both parents working longer hours) may increase the burden of daily activities of parents and children and reduce tolerance for individual variation.

> [P]arents, teachers, and patients may pressure professionals to diagnose under the influence of advertising and ⁄ or the Internet. (p. 492)

8.3.6.5 **"Family therapy/dynamics" in the SMD/TDD/DMDD literature (3 articles)**

Three articles (Leibenluft & Rich 2008; Dickstein et al. 2009; Hulvershorn, Fosselman & Dickstein 2012) mentioned the same three family therapy models that were developed by three PBD researchers. The general focus of these articles was on other interventions and features of PBD and SMD/TDD/DMDD. However, to the extent they noted that family therapy interventions had a place; it is interesting that they each only quoted the same three interventions. The interventions are: *Child- and family-focused cognitive-behavioral therapy* (CFF-CBT) (Pavuluri, Graczyk, et al. 2004); *Mutifamily psychoeducation groups* (MFPG) (Fristad, Goldberg-Arnold & Gavazzi 2002); *Family-focused psychoeducational therapy* (FFT) (Miklowitz et al. 2004). There was no citing of the many family therapy articles and models from outside the PBD literature.

8.3.6.6 **The non-English language articles**

One French language article (Purper-Ouakil & Franc 2011) contained the French equivalent of 'attachment', *attachement,* numerous times in the text and the following segments in its English abstract:

> [C]urrent research highlights the links between emotional self-regulation and executive functions … the role of environmental factors in the development of emotional regulation and self-control. (p. 679)

The remaining 6 English language abstracts from the other non-English articles did not contain any of the search terms.

8.3.6.7 **The one mention of "neglect" – but in a different context**

The term 'neglect' as an aspect of maltreatment did not appear in any of the articles in the SMD/TDD/DMDD literature. However, 'neglect' was used in the article of Batstra et al. (2012):

> A classic criticism against medicalization applies: the 'medical gaze' locates the problem and the place of treatment within the individual child, and *neglects* possible social dimensions of the problem. (p. 493)

8.4 Discussion of literature review

8.4.1 Discussion of the PBD literature

8.4.1.1 Attachment theory almost entirely absent from PBD literature

A systematic review of the PBD literature via searching for the term "attachment" lends credence to critic claims that the PBD literature in general does not address or consider attachment theory concepts. In a large specific sample of PBD related articles, only 15 articles (1.3%) contained the term 'attachment' in an 'all-fields' search, that included title, abstract, keywords and reference list, and only 8 of these 15 articles (0.7% of the total sample) referred to 'attachment' in the text. Three of these eight articles were sceptical of the PBD hypothesis (McClure, Kubiszyn & Kaslow 2002; Carlson & Meyer 2006; Parens & Johnston 2010).

The almost complete absence of attachment theory concepts makes interpretation of trauma and maltreatment/abuse events in childhood problematic. There is evidence that attachment security/insecurity mediates the effects of trauma and abuse upon children (Cook, A et al. 2005).

8.4.1.2 Infrequent coverage of developmental trauma and maltreatment

Furthermore, developmental trauma, maltreatment/abuse and PTSD-related concepts receive infrequent coverage in the PBD literature. The two research institutions that first promoted PBD illustrate this: researchers from MGH-Harvard suggest PTSD mainly arises secondary to PBD, though more recent publications from the group are more cautious; researchers from WUSL report a virtual absence of PTSD in their cohort.

The very low rate of sexual abuse and no cases of PTSD in the WUSL research is remarkable in any clinical cohort. It is also at odds with research (Rucklidge 2006) on a cohort of adolescents in NZ who found 29.2% reported sexual abuse on the same diagnostic instrument used in diagnosing the WUSL cohort, and over 50% of the NZ PBD sample had a trauma history compared with 10% of controls.

8.4.1.3 MGH-Harvard group's theory that PBD leads to PTSD

The MGH-Harvard group propose that PTSD where it is comorbid with PBD arises as secondary to PBD itself. However, the main reference for this, the 1999 study (Wozniak et al. 1999) of

128 peripubertal boys with ADHD, of whom 14 had comorbid PBD, noted a limitation in that PTSD was not assessed for at baseline. Further, from the article it appears that early attachment histories had not been taken in depth, despite the reference to an Israeli study on the importance of the parent-child relationship in buffering trauma. More recent articles (Steinbuchel et al. 2009; Althoff et al. 2005; Faraone, Biederman & Monuteaux 2001) from authors or co-authors affiliated with MGH-Harvard appear open to the possibility of trauma factors causing or exacerbating PBD.

Wozniak et al. (1999) noted several limitations of their study, including that it was of low power. Assuming, however, that there was a definite increased risk for experiencing trauma in the 4-year follow-up period if having a PBD diagnosis, an alternative reading would be that the boys with both ADHD and comorbid PBD at baseline did not have PBD but were in fact exhibiting symptoms of developmental trauma. If that was the case, then the environmental context that had led to their developmental trauma symptoms was likely still present. That then could be a reason why they were more vulnerable to traumatic events over the 4-year follow-up period than those with ADHD but without PBD as defined in the study's methodology.

8.4.1.4 **Siloing of PBD and attachment theory themes in the academic literature**

An 'all-fields' search of a 746-article sample from the attachment theory and developmental psychopathology/traumatology-based literature suggests neglect or dismissal of the concept of PBD. In defence of attachment studies, it could be argued that a large amount of the research has been in early development prior to the onset of typical DSM clinical syndromes, at least as classically defined. However, the absence of reference to the PBD hypothesis is surprising. Further research, comparing PBD with other DSM disorders of childhood, such as ADHD and ASD may help shed light on how much siloing of the attachment/traumatology from the DSM-based descriptive psychiatric literature there is, or whether it is specific to the case of the PBD hypothesis.

The specific case of neuroimaging in PBD research and attachment-trauma oriented research is an example, where similar findings in the attachment/traumatology-oriented literature appear to be interpreted differently by authors from the PBD literature, but without cross-referencing.

There thus appears to be a communication gap between two different paradigmatic approaches in child and adolescent psychiatry and developmental psychopathology. It has been argued that one root cause of this problem lies with the atheoretical symptom-focused approach incorporated within DSM-IV (Denton 2007) and that mainstream psychiatry has become too detached from attachment theory and psychodynamic concepts (Dignam, Parry & Berk 2010). This problem has global aspects but does appear to be more acute in the US.

Rather than existing in disconnected parallel silos, researchers in PBD and other DSM diagnoses may likely benefit from increased dialogue with researchers from attachment theory and developmental traumatology perspectives. Furthermore, attachment-theory-oriented research would be advanced by exploring attachment and trauma influences in DSM-IV and ICD-10 syndromes. Such dialogue may help resolve the intensely controversial nature of the PBD hypothesis.

8.4.2 **Discussion of the SMD/TDD/DMDD literature**

DMDD and its two immediate diagnostic incarnations of SMD and TDD was devised mainly by one group of researchers based at the NIMH. Leibenluft as director of the childhood mood disorders group for the NIMH was well placed to influence DSM-5. Not surprisingly these diagnostic terms have no literature base prior to 2005 and only 76 articles were found searching for the diagnostic labels.

What is striking is that the SMD/TDD/DMDD literature tends to follow the trend of the PBD literature in generally failing to consider attachment theory and pay little attention to developmental trauma and maltreatment factors. Including searches for 'parent' in the context of parenting practices, influences and interventions and 'family' in the context of family dynamics and family therapy again found little consideration for these essential factors affecting child and adolescent mental health. The SMD/TDD/DMDD literature, like the PBD literature, predominantly focussed on phenomenology based in the child's behaviour without consideration of systemic contextual factors. Articles that did draw some attention to contextual factors tended to be critical of the new diagnosis and were also more likely to be from non-US authors. Batstra et al. (2012) included the only time the word *neglect* appeared, to note that contextual factors were neglected in most of the DSM diagnostic labels and the

manner in which they were being applied in much contemporary practice. But child *neglect*, as in a form of child maltreatment, appeared nowhere.

Frances has warned that DMDD may lead to just the same problems inherent in PBD, namely over-diagnosing and overmedicating of children (Frances 2010a). With the academic literature continuing to neglect basic contextual factors such as child abuse, attachment-insecurity and family dynamics, then this scenario is unfortunately likely to come to pass. However, the fact some articles raised these issues suggests that there may be a shift of opinion and some desire to avoid the mistakes of the PBD epidemic.

8.5 Limitations of literature review

This systematic literature review relied on one academic search engine, Scopus; albeit one that aids this form of bibliometric literature search. Defining a body of literature in a sensitive yet specific enough manner proved somewhat challenging. A full reading of all the PBD publications would be needed to make the searches fully accurate. Nonetheless the hypothesis being tested pertains to a broad trend rather than specific articles. In that sense, the use of Scopus in this manner can be justified.

The search of the PBD literature was conducted earlier in the course of this PhD thesis, and the search of the SMD/TDD/DMDD literature was conducted later. The PBD literature search was published as an invited book chapter in an open access online book. I felt that it was important to get this information into the academic and public domain as it points to what I believe is a crucial point in the whole PBD phenomenon: the overly narrow focus on phenomenology in the absence of context. Although I have not formally updated the search beyond mid-2010, the findings show that a decade and a half into the PBD phenomenon, within an ample time frame to consider attachment and trauma factors, this had generally not occurred.

8.5.1 Addendum: Search 'attachment' in PBD literature 2010-2013

The SMD/TDD/DMDD literature is more recent and became particularly topical by the time of DSM-5's launch at the 2013 APA conference in San Francisco. I presented the findings of this literature review on both diagnoses at the APA meeting (Parry 2013). In doing so I partially updated the search by performing the same high-specificity Scopus search for *'attachment'*

in the PBD literature from June 2010 to March 2013. Articles in this high-specificity search increased by 323: from 1,113 in June 2010 to 1,436 in March 2013. Out of these 323 articles only 6 contained 'attachment' in an 'All Fields' search. These 6 were:

1. Our own article (Parry & Levin 2012) titled "Pediatric bipolar disorder in an era of 'mindless psychiatry'" (Appendix A18).

2. A Canadian/German article authored article (Lewitzka et al. 2012) titled "Biological indicators of suicide risk in youth with mood disorders: What do we know so far?". This article had attachment in the passage:

> There has been growing interest in other psychosocial and environmental factors associated with suicidality such as attachment, personality, [*12, 13*], self-concept [*14*], and adverse life events including bullying and peer victimization. (p. 705)

3. An article in *JAACAP* (Keenan-Miller et al. 2012) that included Miklowitz as an author and hence examined family aspects in PBD. The article was titled: "Family functioning, social impairment, and symptoms among adolescents with bipolar disorder". The word 'attachment' only appeared in a reference title; however, the reference was cited in the text for the passage:

> Links between child aggression and negative family dynamics are well-documented and typically conceptualized as bi-directional in nature. (p. 1091)

4. An article by Iranian and Swiss authors (Bajoghli et al. 2011) noted that in female adolescents, romantic love is related to hypomanic-like stages and increased physical activity, but not to sleep or depressive symptoms. 'Attachment' was only in a reference title, cited in the text for the statement:

> Across cultures and epochs, falling and being in love has been described as a cross-cultural universal. (p. 164)

5. The term 'attachment style' appeared in a list of factors in an article titled: "Generation of life events in bipolar spectrum disorders: A re-examination and extension of the stress generation theory" (Bender et al. 2010):

> In unipolar stress generation, researchers have identified a number of potential mediators and moderators of the process, including poor interpersonal problem solving (Davila et al., 1995) or social skills (Segrin, 2001), excessive reassurance

> seeking (Joiner, Wingate, Gencoz et al., 2005), attachment style and personality variables (Hankin et al., 2005; Nelson et al., 2001; Shih, 2006), cognitive styles (Safford et al., 2007), and hopelessness (Joiner, Wingate, & Otamendi, 2005); it will be important to examine the role of such constructs in bipolar event generation as well. (p. 923)

6. The sixth article (Bradfield 2010) titled: "Bipolar mood disorder in children and adolescents: In search of theoretic, therapeutic and diagnostic clarity" in the *South African Journal of Psychology* by a University of Cape Town psychologist accepted the PBD constructs, heavily citing US PBD researchers such as Pavuluri. It did cover attachment theory in a little more depth, referring to similarities between bipolar disorder and borderline personality disorder and "right brain structures" associated with emotional dysregulation and early attachment:

> What is interesting to bear in mind in considering the aetiology of bipolar disorder and the documented diagnostic blurring of the borderline/bipolar classification is the notion that those right brain structures that function in the regulation of emotion develop in the first 18 months of life. Their normative development is promoted by the presence of a growth-facilitating emotional environment that is provided by a secure attachment relationship with a primary caregiver (Schore, 2000). This insight is interesting, considering the observation that borderline personality disorder is connected aetiologically with trauma in the context of early attachment relationships (Fonagy, Target, Gergely, Allen, & Bateman, *2003;* Herman, Perry, & Van der Kolk, 1989; Holmes, 2004). Both bipolar and borderline presentations are characterised by instability of affect regulation; a feature which makes them appear quite similar. (p. 243)

Thus, it would seem that the PBD literature continued to ignore attachment theory until 2013 at least. To know whether it has continued to pay similarly low rates of attention to maltreatment, abuse, neglect and trauma/PTSD factors would need a further literature review.

PART III – DISCUSSION OF THE PBD PHENOMENON

This thesis examines a complex controversial subject across a lengthy time-frame. Contributing factors included the influence of the pharmaceutical industry, the managed care health system in the US, editorial perspectives taken by key journals and the media, promotion by a large online advocacy group, the role of the DSM-5 child and adolescent mood disorders committee and a dominant biomedical paradigm in sections of US psychiatry. The debate internationalised and evolved over time. Given these factors, a standard critical literature review on its own could not do justice to the issue of why the PBD hypothesis had been reified so quickly and became a geographically-based epidemic that normalised psychotropic medicating of toddlers. Consequently, a narrative history comprised Part I, similar to the detailed and complex case history from several sources as has been generally customary in child psychiatry.

In the process of personally engaging in the international debate over PBD for more than a decade, and writing the narrative account of the PBD story, three research questions emerged and were addressed in the novel research in Part II. This research found that: bipolar disorder in the paediatric age range was not as common as claimed. A geographic divergence in views on PBD became apparent. Further, the PBD literature neglected pertinent contextual factors of attachment and developmental trauma. These findings not only challenge the validity of the PBD hypothesis but have significant implications at a much broader level. In particular, the iatrogenic consequences of the PBD epidemic raise issues of medical ethics. The PBD phenomenon also raises questions for the field of psychiatric nosology that failed to restrain the PBD hypothesis from rapid translation into clinical practice in large parts of the US and some international centres.

In order to bring the many strands of the PBD phenomenon together, a ‘dynamic diagnostic formulation’ as a conclusion was found to be a useful framework. The dynamic formulation method is a core approach to understanding complex systems impacting on patients in

psychiatry, and to an extent in general medicine. A diagnostic formulation assists in identifying the most likely contributory factors as to 'why does a patient develop a problem or syndrome at a particular point in time?' The RANZCP "Clinical Examinations Formulations Guidelines for Trainees" (RANZCP 2012) state: "The ability to formulate a case is one of the most important skills of a consultant psychiatrist" (para. 1). The process of diagnostic formulation involves "hypothetico-deductive logic" and provides a structure for various putative causative or contributory factors from different domains and their interactive effects (Nurcombe & Fitzhenry-Coor 1987, p. 477). As in clinical practice, this 'formulation' provided a framework to explore how and why the PBD epidemic manifested in the manner and time it did. Continuing in the tradition of RANZCP training and practice, the discussion encapsulated in Chapter 9 leads to a conclusion with a diagnostic formulation leading into a proposed management plan to assist in addressing the issues raised by the PBD phenomenon.

CHAPTER 9. CONSEQUENCES AND IMPLICATIONS OF THE PBD PHENOMENON

9.1 Implications of the novel research

9.1.1 Van Meter et al. meta-analysis re-examined

The Van Meter et al. meta-analysis has been used as a powerful vehicle for perpetuating the PBD hypothesis that early childhood bipolar is common. The very fact that the 1.8% community prevalence figure for 'children and adolescents' is cited in the DSM-5 (p. 136) is testament to how widely this myth has spread. This rate was increased by the ISBD Task Force on PBD to 2.06% and then further to 3.9% in an updated meta-analysis (Van Meter, Moreira & Youngstrom 2019b).

Since the time of Kraepelin, the classical view has been that age of onset of bipolar disorder is almost always from late adolescence onwards, with only rare sporadic earlier onset cases. Kraepelin claimed 0.4% of his cases of manic-depressive insanity presented by age 10 and cumulatively 2.9% by age 15 (or age 16: Kraepelin's table is unclear) (Chapter 2.1). This data presumably came from retrospective reports, and one quarter were listed as having depressive episodes, so strictly speaking could not be defined as bipolar disorder until later.

Extrapolating from a lifetime prevalence for Bipolar-I disorder of 0.49% (Ayuso-Mateos 2006) or 0.6% (Merikangas et al. 2011; Chapter 1.3) and Kraepelin's figures, then the community prevalence of Bipolar-I for under-15 (16) year-olds should be 0.014% to 0.017% or less (given that a proportion would have had only a depressive episode). This figure derived from classical prevalence rates is more consistent with the recent large epidemiological studies that included pre-adolescents in their cohorts. These include: the British studies by Stringaris, Santosh et al. (2010) that found a rate of 0.028% of Bipolar-I/II disorder for 8 – 15-year-olds and Vizard, Pearce et al. (2018) finding 0% in 5 – 16-year-olds; the Turkish study of 7 – 10-year-olds that found 0% bipolar spectrum disorder (Karacetin et al. 2018); and the Brazilian studies that found 0% cases of bipolar spectrum disorder in 11 – 12-year-olds (Anselmi et al. 2009) or 0.2% of Bipolar-I/II cases increasing to 1.4% (weighted prevalence) when including the softer bipolar spectrum cases although the authors debated the validity of the non-Bipolar-I/II cases (Pan et al. 2014; Pan, Salum & Bressan 2019). This estimate is also consistent

with the diagnostic rates from paediatric psychiatric inpatient units in the UK, Germany, Denmark, Finland, Czech Republic, Australia, and New Zealand (Chapter 4.8.6.14). Similarly, it is consistent with four of the longitudinal high-risk offspring studies that so far have found no under-12-year-olds and almost no early adolescents (Chapter 4.8.7). The Swiss study did find six younger offspring with mania or hypomania; however personal communication (C Van Der Leur, 2018, email, 17 February) confirms that these uncommon cases were subject to significant 'domestic trauma' and had not had recurrences of mania in the years since. This implies that severe trauma may precipitate an early onset of true hypomania/mania or produce an acute stress reaction that has similarities but would be better understood as Developmental Trauma Disorder (although rejected by the DSM-IV and DSM-5 committees) or the ICD-10 diagnosis 'Other reactions to severe stress'.

The examination of Van Meter et al.'s meta-analysis in terms of methodology, and examination of the original epidemiological surveys, point to the validity of the classical view. Carlson's (2018) commentary on the re-examination of the meta-analysis notes:

> The premise of the meta-analysis [was] to debunk the notion that BP disorder are higher in the US than elsewhere … [but] ... Parry et al debunk the debunking and present data that the conclusions are false. (p. 23)

If as it appears, these community prevalence figures of 1.8% to 3.9% used as a cornerstone by PBD proponents is based on incorrect data and conclusions, then it severely undermines the validity of the PBD hypothesis. As concluded by Duffy and Malhi (2017) in their *ANZJP* editorial on the longitudinal offspring studies, the phenotypes described by the PBD hypothesis are not related to the development of bipolar disorder in high-risk offspring. In light of both the offspring studies and the reanalysed epidemiology it was suggested the debate over PBD may be heading for resolution and "it would be preferable to dispense with the term 'PBD' at this stage" (Parry, Allison & Bastiampillai 2018c, p. 901; Appendix A30):

9.1.2 **PBD as a US phenomenon**

In writing the narrative history, reading the literature, attending conferences, and participating in the debate on PBD in both the literature and through presentations and discussions with colleagues, it appeared that the PBD hypothesis has remained mostly confined to parts of the US. Nonetheless some PBD researchers had at times expressed

frustration that PBD is viewed as an “American problem” (Youngstrom et al. 2012), and the ISBD Task Force aimed to dispel the “myth” that there was “no evidence outside of US for [PBD]” (Goldstein et al. 2017, p. 529). While it is true that a small number of international academic centres had embraced the PBD hypothesis in collaboration with US PBD researchers, the above sources suggested that the majority of world child psychiatrists continued to hold the classical perspective and were sceptical of the PBD hypothesis.

The salient task that emerged was to identify what research approach could confirm or disconfirm this impression. The methodology of bibliometrics, supported by increasingly sophisticated academic search engines enables such questions to be examined in more quantifiable ways. The *Web of Science* search engine and database allowed for a ‘citation tree’ body of PBD literature, in which institutional and national affiliation of authors could be identified. However, on a topic of such heated controversy, a simple bibliometric count of such articles would not provide the necessary information as regards the acceptance or non-acceptance of the PBD hypothesis. Therefore, articles were given simple designations according to their perspectives on the PBD hypothesis. While this was a subjective exercise based on personal interpretations of abstracts and full articles, the simplicity of the categorisation into for, against, traditional or not related lessened the risk of bias; further the categorisation can be verified by others in the data provided in Appendix C of this thesis, and in the online supplementary files to the published article (Parry, Allison & Bastiampillai 2019b; Appendix A35).

The findings confirmed the impression that the critical literature review and narrative journey through the history of the PBD epidemic had engendered: the PBD hypothesis remained mostly confined to several US academic child psychiatric centres. What is interesting is the impact these several centres were able to exert for so long upon US child psychiatry. This suggests the presence of networks of influence involving pharmaceutical sponsorship, CME, AACAP and key journals within the US. Those few centres outside the US supporting the PBD hypothesis had direct collaboration with US PBD researchers. The reasons for this have implications for the paradigm of psychiatric nosology and application of ethics in research and these aspects are explored below.

9.1.3 **PBD research lacked consideration of context**

A bibliometric analysis of a large body of PBD literature using the academic search engine and database, *Scopus*, was used to test the question of whether or not attachment theory was being neglected. The findings confirmed that attachment theory was almost totally absent in the PBD literature; maltreatment and specific child abuse terms were infrequently addressed; and detection of maltreatment factors in clinical PBD cohorts was vastly lower than community prevalence rates. The WUSL group found no cases of PTSD and only mentioned sexual abuse as a differential diagnostic consideration to 'manic hypersexuality'. Only 1% of their PBD cohort had a history of sexual abuse. This very low rate is at odds with the literature on child sexual abuse and is also low compared to a study of narrow phenotype PBD using the same diagnostic methodology, that found more than 50% had a trauma history and 29% of sexual abuse (Rucklidge 2006, p. 185). The MGH-Harvard group referenced Wozniak et al. (1999) in hypothesizing that PTSD occurs secondary to PBD. They theorised that a child develops PBD early in childhood and their subsequent behaviour leads to stressful situations and the child being traumatized. However, this theory is at odds with a large body of early attachment and infant psychiatry literature (for example: Amos, Segal & Cantor 2015; Cook, A, et al. 2005; Schore 2003a; Teicher & Samson 2016; van der Kolk 2005).

A similar search of the smaller SMD/TDD/DMDD literature also revealed a lack of contextual factors including parenting and family dynamic factors. The PBD and SMD/TDD/DMDD literature cite only three family therapy approaches, all devised within the PBD research community and focused on acceptance of PBD as a valid entity within a family framework, ignoring the vast family systems theory and family therapy literature pertinent to understanding and helping affectively and behaviourally dysregulated children, adolescents and their families.

This neglect of attachment and trauma is returned to below as there are implications for iatrogenic consequences of missed childhood maltreatment and by corollary medical ethics, as well as contributing to a superficial truncated psychiatric nosology. As Nurcombe and Fitzhenry-Coor (1987) state, one "trap" of bypassing the biopsychosocial model is that "categorial diagnosis is pursued to the exclusion of dynamic formulation and treatment planning is reduced to prescribing for syndromes" (p. 482).

A real-life case will illustrate just how severe the iatrogenic consequences of truncated descriptive psychiatric diagnosing practices can be. 'Adam' (not his real name) was introduced in the Prologue (p. 13) and his story in his own words was published (Parry 2014a, Appendix A26). Excerpts of 'Adam's' story are quoted in the following sections.

9.2 PBD as an iatrogenic hazard

> *The (PBD) diagnosis has spread too broadly, so that powerful drugs are prescribed too widely...we are going to have hell to pay in terms of side effects.*
>
> Steven Hyman, former director of the NIMH
> (quoted in Groopman 2007, p. 30)

9.2.1 The neglect of contextual factors and other causes

If the diagnosis is wrong, the treatment is also often wrong. Kaplan in his book *Your Child Does NOT Have Bipolar Disorder* argued the converse to Biederman's 1998 *JAACAP* Debate article by asserting that ADHD was often mistaken for mania during the PBD era. He commented (Kaplan 2011b):

> Influential advocates of the pediatric bipolar diagnosis have advised that stimulants make bipolar disorder worse and should not be used … This poor advice often results in preventing children diagnosed with bipolar disorder from receiving the very medication that could improve their symptoms most (McIntyre, 2009). (p. 129)

Harris (Chapter 4.8.2.9) described two cases in her article of PBD-diagnosed children, where the correct diagnoses were autism on one hand and domestic trauma on the other (Harris, J 2005). Carlson and Meyer (2006) also described a series of cases, some that did have true bipolar disorder, others with mixtures of ADHD, learning disorders and developmental trauma that were not being treated appropriately as the PBD label was obscuring the true diagnostic factors (Chapter 4.8.3.2). They concluded:

> [T]he diagnosis of bipolar disorder is often made by mindlessly applying criteria, and without carefully listening to the informant and child to ascertain what they mean by the examples they give of various symptoms, and without understanding developmental history and context. (p. 962)

‘Adam’ described a range of family contextual factors that he says were never addressed by his psychiatrist over the seven years he carried the PBD label and was being prescribed up to eight psychotropics concurrently:

> I come from a screwed-up family and was physically abused by a sibling. Parents divorced young. My mother had a lot of issues, *etc.* So it goes without saying there was a lot the psychiatrist should have asked if he was ever so inclined. (p. 336)
>
> Many of the arguments with my mother that would land me in hospital began several hours before as an argument solely about wanting to stop my medicines. There is always context. (p. 337)

As Adam stated, “there is always context”. This decontextualized assignation of a diagnostic label during the PBD epidemic is explored in greater depth in relation to implications for psychiatric nosology below.

9.2.2 **Psychotropic medication related morbidity and mortality**

‘Adam’ described receiving a copious amount of psychotropic polypharmacy from age 12 until he left home at age 19. He also described serious adverse-effects. The treatment ‘Adam’ received would be highly irregular in Australia and possibly trigger medical board investigation, yet ‘Adam’ informed me his treatment would be deemed “standard practice” where he lived (Parry 2014a, p. 341). Nonetheless there are reports of iatrogenic morbidity and mortality from such medication regimes in the US media and academic literature. A health system that forces many child psychiatrists into brief ‘med checks’ is seen as a serious problem by many US colleagues (e.g. Williams 2008).

Chapter 4.6.4 covered research by journalists from *The New York Times* (Harris, G 2007; Harris, G 2008a) and *USA Today* (Elias, 2006) that found scores of children were dying and thousands with serious adverse effects that had been reported to the FDA’s Adverse Event Reporting System FAERS where antipsychotics, principally the atypical antipsychotics, were named as ‘primary cause’. Given that a systematic literature review reports a “median under-reporting rate [of adverse drug reactions] across 37 studies [of] 94% ... from medical doctors and other health professionals” (Hazell, L & Shakir 2006, p. 385-6) and that the time scales the journalists examined were limited due to the large size of the FAERS database, these

numbers could probably be multiplied across the past two decades for the US. This investigative journalism used similar research methodology (G Harris, 2008, email, 23 December) as academic research which found atypical antipsychotics figure highly as a 'primary cause' of death in all age groups on FAERS (Moore, TJ, Cohen & Furberg 2007). The lead author of the academic research said in an email that they had not assessed mortality and morbidity from medications by age but he suspected that "psychoactive drugs account for a very substantial fraction of serious injuries and deaths in the 5 – 17-year-old age group" (TJ Moore, 2008, email, 2 November). The media cases of Rebecca Riley and Destiny Hager (Chapters 4.5; 4.6.4) put a human face onto a phenomenon that may have affected hundreds of other children. 'Adam' described the adverse drug events he suffered, in some detail, for example:

> I always had terrible sedation from the anticonvulsants and atypical antipsychotics. The sedation from divalproex was unmanageable and had a deadening effect. When I was initially on 7 or 8 drugs, I had terrible tremors, severe memory problems and my head was about as functional as a block of lead. (Parry 2014b, p. 338)

Metabolic adverse effects with atypical antipsychotics have been found to increase with psychotropic polypharmacy (Burcu et al. 2017). Foster children received a particularly high level of psychotropic medication, as well documented in the state of Texas (Zito et al. 2008) where 430 children in foster care in 2004 "were prescribed antidyskinetic drugs to control side effects from antipsychotics" (p. 77) (Strayhorn 2006). As mentioned (Chapter 4.8.4.2), large numbers of young children have been reported as receiving atypical antipsychotics, for example 42,459 American 1 – 6-year-olds in 2006 (Olfson, King & Shoenbaum 2015).

The situation led to laws being promulgated for authority requests prior to prescribing in several US states, and once enacted, these laws saw dramatic falls in the rate of prescribing particularly to very young children (Schmid, Burcu & Zito 2015; Barclay et al. 2017). However, Kaplan in a post to his *Psychology Today* blog, argued that such well-intentioned 'central planning' can have deleterious consequences leading to children with severe violent aggression not getting the adjunctive antipsychotic medication that can be beneficial and pushing clinicians into further diagnostic upcoding to PBD (Kaplan 2016).

There is a difference in harms from atypical antipsychotics prescribed for children diagnosed with PBD and stimulants such as methylphenidate prescribed for children with ADHD. The latter have a cognitive performance-enhancing benefit and can produce significant benefits for children who truly do meet full criteria for ADHD, although the ethics of diagnosing and medicating for ADHD remain complex (Singh, 2008). In contrast, the harm to benefit ratio is weighted towards iatrogenic harms in the case of atypical antipsychotics in nearly all children without psychosis (Daviss et al. 2016). A PBD diagnosis was often accompanied by a prescription of an atypical antipsychotic.

9.2.3 **The iatrogenic harm from erroneous labelling**

In addition to physical morbidity and mortality, there can be adverse effects on a young person's self-concept and psychosocial development from an erroneous label of PBD (Purcell 2007). It can also be argued that parent-child communication is constricted in meaning if reduced to, or overly focused upon, the vocabulary of mental symptoms and medication**.** While there has not been specific research on this in PBD, there has been some in the case of ADHD, and even where children and adolescents acknowledge benefit of stimulants for concentration at school, many feel stigma, that "medication took away a feeling of exuberance that was part of their identity" (Brinkman et al. 2012; p.) and reluctance taking medication was common with 30 of 48 children in one study expressing a negative opinion in spite of improved concentration for most (Sleator et al. 1982). Floersch and colleagues in an in-depth questionnaire (Teen Subjective Experience of Medication Interview) of 20 adolescents about their psychotropic medication found mixed opinions, nine had a diagnosis of bipolar disorder and a case vignette was described where a 14-year-old girl, 'Alicia', saw her psychotropic medication as helpful for her family because she was less angry but "not so much" for her. She described no classical manic symptoms but simply emotional distress, sibling rivalry and some oppositionality in the context of a bereavement of her beloved grandmother and family's subsequent forced move from the grandparental home. Her grief was labelled 'separation-anxiety disorder' and behaviour as 'bipolar disorder'. Alicia initially disbelieved these labels but after eing persuaded by the paediatrician and online information she then reluctantly reconciled herself to life-long medication (Floersch et al. 2009).

The central task of adolescence is identity development (Erikson 1993), which could be severely compromised by misdiagnosis with PBD, where every thought and feeling can be doubted as being truly part of self. 'Adam' eloquently described all these effects, as well as the impact of sedating medications on his subjective experience. He required psychotherapy to facilitate his working through the labelling effects of PBD, the detachment from his teen years due to heavy sedation as well as the real but never-addressed family dynamic aspects of his growing years. As 'Adam' said: "Everything in [his] life was screened through the filter of this immaterial 'disease'" (Parry 2014b, p. 337).

This damage to identity formation in children with PBD diagnoses has been noted by Batstra and colleagues, who outline six ways the child and growing young person's identity can be damaged by a medicalisation of emotional and behavioural issues: (1) reduced parental and teacher expectations; (2) stigma and discrimination by others; (3) self-stigma resulting in low self-esteem and self-efficacy; (4) later difficulties with employment and life insurance and so forth; (5) disempowerment of the child's voice; and (6) a spurious impression of understanding and false sense of confidence so that deeper causes are not explored (Batstra et al. 2012, p. 493).

Thousands of young adults who've grown up with the PBD diagnosis do not have the resources 'Adam' had marshalled. With PBD and other such inaccurate diagnoses psychiatrists are often faced with having to 'undiagnose' patients and, given the entanglement of label with identity, this requires much tact and support, as an article on the art of 'undiagnosing' explains (Patfield 2011). It is an area that warrants further research.

One of the principle tenants of medical ethics is enunciated in the Latin term *'primum non nocere'*: first, do no harm. The PBD diagnostic epidemic led to breaches of this through: 1) missing real-life contextual stressors and diagnoses; 2) inappropriate use of psychotropic medications, particularly atypical antipsychotics, with serious adverse events; and 3) distorting effects on self-identity, family and social systems of labelling emotions and behaviours of children and teens as driven by bipolar disorder when they were not. A deeper reflection on the ethical implications provides further insights.

9.3 Ethical implications of the PBD epidemic

9.3.1 The principles underpinning medical ethics

According to Beauchamp and Childress (2009), in their seminal textbook *Principles of Biomedical Ethics*, the "four clusters of moral principles" undergirding medical ethics are:

> (1) *respect for autonomy* (a norm of respecting and supporting autonomous decisions); (2) *nonmaleficence* (a norm of avoiding the causation of harm), (3) *beneficence* (a group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs), and (4) *justice* (group of norms for fairly distributing benefits, risks, and costs). (p. 13)

If PBD is in fact an erroneous diagnosis, as the three research pieces and narrative history suggest, then there are some extreme ethical implications associated with each of these clusters.

9.3.1.1 Respect for autonomy

Autonomy concerns the right of a patient to informed consent and to refuse treatment as long as their mental condition does not render them under the restraints of a mental health act treatment order. In the case of children and young adolescents, parents or other guardians are in a position to make treatment decisions on the child's behalf. For ethical treatment, guardians and prescribers must be acting with full beneficence and no maleficence in the full interests of the child. However, with child behaviour problems, guardians and other carers may have mixed motives. It is vital that practitioners take time to make thorough diagnoses. This requires hearing the child's voice in an appropriate therapeutic setting with sufficient time and number of sessions for the child to feel safe to divulge his/her inner world and relevant contextual experiences.

As discussed in Chapter 4.8.3.4, the diagnosis of PBD was often made in research settings on the basis of parent informant alone via a standardised questionnaire, and ignored the voice of the child. In clinical practice, the abbreviated time for assessment set by parts of the US health system also diminishes the child's autonomy and capacity to provide his/her story, as well as the voice of the parent. The case of 'Adam' illustrates an adolescent's frustration over a period of years seeking to have his voice heard.

9.3.1.2 **Non-maleficence and beneficence**

The issue of iatrogenic harm, as described above, indicates that the principles of non-maleficence (*primum non nocere*) and beneficence have been many times abrogated in the case of PBD, through both prescribed medications and stigma through labelling. It also happens when an erroneous diagnosis of PBD ignores psychosocial contextual factors that are then not addressed, or obscures other disorders that are then neither diagnosed nor properly treated.

The widespread use of atypical antipsychotics for PBD, and disruptive behaviour disorders in general, is concerning. As the chief-editor of the *British Journal of Psychiatry* noted, the risk/benefit ratio requires a very serious mental illness, even in adults, to warrant their prescription (Tyrer 2012):

> The combination of extrapyramidal symptoms, dangers of tardive dyskinesia and the neuromalignant syndrome, weight gain and the metabolic syndrome, sedation, postural hypotension, and interference in sexual function … would need to be offset by massive symptomatic and social functioning improvement to make the benefit/risk ratio positive. (p. 168)

In addition to those adverse effects, evidence continues to accumulate that antipsychotics cause cerebral atrophy. A prominent study of long-term antipsychotics for schizophrenia provided strong evidence that brain volume loss, including of prefrontal cortex, results from the antipsychotics as well as the underlying disease in human (Ho et al. 2011) and juvenile animal (Dorph-Petersen et al. 2005; Vernon et al. 2011) studies. Other mammalian studies indicate disruption of serotonin (Choi et al. 2010) and dopamine (Moran-Gates et al. 2007) receptors when low dose risperidone was given to juvenile rats, whereas only high dose risperidone had this effect in mature rats. Risperidone-treated juvenile rats were hyperactive as adults (Bardgett et al. 2013) while risperidone-treated juvenile monkeys, with age equivalence to 4 – 8-year-old children, after four months had increased perseverative errors that were deemed permanent in the 4-month follow-up period (Mandell, Unis & Sackett 2011).

This data raises the disquieting possibility that millions of children have now experienced neurological retardation and dysregulation from atypical antipsychotics globally. The

cost/benefit ratio may have met beneficence in some cases of severe autism and true mania, and brief periods of extreme aggression as argued for by Kaplan (2016). But it seems likely that the principles of non-maleficence and beneficence have been seriously breached in the case of atypical antipsychotics for PBD.

One of the greatest scandals in the history of psychiatry, although initially considered revolutionary, was the practice of performing prefrontal lobotomies on thousands of patients from the 1930s to 1960s. It started in Portugal as a Nobel Prize winning treatment to reduce extreme agitation in schizophrenia. It was championed in the US by psychiatrist Walter Freeman who expanded the indications to any serious mental illness, and then to CD and ODD type problems. He performed lobotomies on 19 minors including one 4-year-old child, before the procedure fell into disrepute (Encyclopedia Britannica 2017; Rogers 2015).

The neurological harms of lobotomies were much greater than those from psychotropic polypharmacy, however juvenile mammalian studies revealing growth retardation of prefrontal lobes from consumption of atypical antipsychotics do raise a disquieting prospect of a similar, albeit milder problem. This is a subject requiring urgent research, given that millions of children and adolescents around the world are receiving atypical antipsychotics.

JAACAP treatment guidelines of 2005 (Kowatch et al. 2005) and the ISBD Task Force on PBD (Goldstein et al. 2017) advocate for atypical antipsychotics as first-line treatment for PBD and suggest that classical child mental health interventions such as parenting support, individual therapy family therapy and social supports are merely adjunctive. This is of substantial concern if many of these PBD cases are not true Bipolar-I disorder.

9.3.1.3 **Justice**

The medical ethical principle of justice concerns the right to health care and for health care to be equitably distributed within a society. The US health care system has been criticized for not meeting this principle: the issues that defy this principle include ‘diagnostic upcoding’ pressures, brief ‘med check’ appointments in psychiatry and paediatrics, and insurance companies favouring pharmacotherapy over individual, parenting and family therapy (Chapter 4.6.9; 4.8.2.26). These reasons may help explain why the PBD hypothesis translated into clinical practice in parts of the US but much less so in Australasia and parts of Europe, given the different healthcare systems in place.

9.3.2 **Scientific ethics appear breached in PBD epidemic**

The US Senate Finance Committee inquiry into financial relationships between the pharmaceutical industry and health care organisations and practitioners carried a clear implication that conflicts of interest between PBD researchers and the pharmaceutical industry that was providing substantial funding to them were a factor in the spread of the PBD hypothesis (Levin & Parry 2011; Appendix A15; Chapter 4.8.2.26).

The scientific method itself is compromised and scientific ethics of integrity and proper processes of inquiry are breached when research is designed to yield results that conform to pre-existing expectations. This appeared to be the case (Chapter 4.8.2.20) at the 2009 AACAP conference when a prominent PBD researcher said she could not use a more diagnostically agnostic term such as 'affect dysregulated' for her neuroimaging subjects. She replied: "if we don't call them bipolar, we won't get funding for our research" (Pavuluri 2009; M Pavuluri, 2009, direct quote during her AACAP presentation, 28 October). Promising sponsors results that would "move forward the commercial goals of J & J" was listed as the third main criteria for research at the "Johnson & Johnson Center for Pediatric Psychopathology at the Massachusetts General Hospital" (Chapter 4.2.7). In conjunction with the media and litigation-exposed email anomalies between a Janssen employee and Biederman, the director of the centre, it can be seen how scientific research ethics appear to have been compromised. These are serious ethical concerns, as the extraordinary editorial in the *American Journal of Psychiatry*, in the wake of the Grassley inquiry and other revelations states:

> Our ethical principles as physicians are designed to protect our patients in many ways— *primum non nocere,* confidentiality, prohibitions of boundary violations. We now need to protect our patients from conflicts of interest in the selection of their treatment. (p. 275)

Further discussion of conflict of interest and issues of justice in health systems and their role in the spread of the PBD epidemic are explored below.

9.4 Why did the PBD epidemic occur?[4]

9.4.1 The battlefield of psychiatric nosology

> *Taxonomy is described sometimes as a science and sometimes as an art, but really it's a battleground.*
>
> Bill Bryson
> *A Short History of Nearly Everything,* p. 360

9.4.1.1 PBD as emblematic of a war-torn nosology

In psychiatry, the 'taxonomy' is the classification of disorders, referred to as nosology. As Ghaemi and Martin (2007) editorialised, "Pediatric bipolar disorder is notoriously controversial" (p. 185), but PBD is not an isolated example. The history of psychiatric nosology has been marked by fierce debates and controversies. The fractious discourse within psychiatric nosology flows from the lack of clear biomarkers and the subjective aspect to psychiatric diagnosis.

It would be a relief if psychiatry were at the stage of some other medical specialities, no longer dealing with categorising types of 'fever', was beyond identifying syndromes, and had a classificatory system validated by, for example, laboratory tests, biopsies and imaging studies that required less consideration of context or patient history. However, it does not, and given the perhaps irreducible mind/brain problem this may never be the case for many 'disorders'. The 19th-century style classificatory system of syndromes is the best we have for most disorders, and so there is a constant risk of prematurely reifying syndromes into concrete disease entities (Parry 2009b; Appendix A9). A problem with PBD is that it is not just a prematurely reified syndrome: that could be said of many disorders in the DSM and ICD, for example the DBDs: ADHD, ODD and CD. The problem is PBD is a reified hypothesis (Parry, Allison & Bastiampillai 2015; Appendix A28). Further, the symptoms in the PBD 'syndrome' are also described in other diagnostic categories/syndromes.

[4] This sub-chapter contains transcripts from published articles: Parry (2009b; Appendix A9); Dignam, Parry and Berk (2010; Appendix A12); Parry and Levin (2012; Appendix A18); Parry (2014a; Appendix A26).

Frances (2010b) criticised the researchers proposing the PBD hypothesis for "ignoring the DSM-IV definition in favour of a new and largely untested idea that Bipolar Disorder presents very differently in children" (p. 1). While the PBD hypothesis entered the DSM via the Bipolar-NOS category, its proponents then advanced to claim territory of Bipolar-II and Bipolar-I categories based on the idea cited above, that "Bipolar Disorder presents very differently in children" (p. 1). Their success can be seen in the title "Prospective continuity with adult bipolar-I disorder" of the Geller et al. (2008) highly cited 'article of the year' in *Archives of General Psychiatry* (Chapter 4.8.2.15).

Frances implies this should not have happened. Yet it did. The boundary defences of DSM diagnostic criteria may appear strict and secure in the manual, but in the real world they can be vague and variably applied. That this happened with PBD warrants a deeper look into psychiatric nosology in order to understand the furore over this hypothetical diagnosis. A useful starting point lies in examining what is taught to psychiatrists in their training.

9.4.1.2 Psychiatric training and diagnostic formulations

> *It is as important to know the man who has the disease as it is to know the disease the man has.*
>
> Hippokrates

Emeritus Professor of child and adolescent psychiatry at the University of Queensland, Barry Nurcombe has been a mentor to many in the area of psychiatric nosology. Nurcombe has a chapter titled "Diagnosis and treatment planning in child and adolescent mental health" in the *IACAPAP e-Textbook of Child and Adolescent Mental Health* (Nurcombe 2014), that includes a grid familiar to most psychiatry trainees (Figure 9.1).

Figure A.11.1 Integrating the data as a diagnostic formulation: the diagnostic matrix

	Predisposition	Precipitation	Pattern	Perpetuation	Potential
Physical					
Psychological					
Family/Social					

Figure 9.1: Integrating the data as a diagnostic formulation: the diagnostic matrix (Nurcombe 2014, p. 5)

DSM criteria are often limited to just the 'pattern' section. The full grid illustrates how limited that slice of knowledge is. In the hundreds of PBD research articles examined in this thesis it becomes clear that the 'evidence-base' is mostly from that narrow sliver, gleaned through structured interviews or survey questionnaires that focus almost entirely on symptoms.

In the Queensland Child and Youth Mental Health Service, where I am employed, electronic patient records require 3-monthly case reviews, where the case-manager/primary therapist must complete a full diagnostic formulation, a system initiated by Professor Nurcombe. It means all psychiatrists and allied mental health workers 'speak the same language' based on a developmental and contextual understanding of our patients' problems and disorders.

However, this system is not utilised systematically around the world. Nearly 30 years ago, at the start of my psychiatry training, Sydney based Professor Derek Silove published his observations on a "recent study trip to North America" in the *ANZJP* (Silove 1990). Under the title "Biologism in psychiatry" Silove described a narrowing of psychiatric training in the US:

> In the area of teaching, North American clinicians schooled in more comprehensive clinical traditions of yesteryear, express fears that training programmes in psychiatry offer little more than instruction in matching formula-based "diagnoses" to specified pharmacological treatments. (p. 461)

Silove was hopeful Australasian psychiatry's grounding in the biopsychosocial model could buffer it from 'biologism'. In the years since Silove's warning, Australian and New Zealand psychiatrists in training have still had to pass written case histories, including long-term psychotherapy cases. The oral viva exam still incorporates 'long cases' with real life patients. In these exams the provision of a 'dynamic diagnostic formulation' is considered imperative, a time-honoured way of understanding a patient's difficulties. It allows the clinician to be able to answer the question: "Why does the patient present with these symptoms at this time in their life?" The answer to this question derives from the unique real life of the patient and permits the development of a therapeutic management plan tailored to their needs.

Echoing Silove's opinion, professor of psychiatry at the University of Louisville, Kentucky, Allan Tasman wrote of US psychiatry training (Tasman 1999):

> Many fear that we are in danger of training a generation of psychiatrists and physicians who lack basic psychotherapeutic skills or a framework for understanding mental functioning from a psychodynamic perspective. (p. 189)

The loss of the biopsychosocial diagnostic formulation, that includes a psychodynamic formulation of a patient's symptom complex, appears to have followed the demise of psychodynamic theory in US psychiatric training, at least in some states. In practice, this means that the surface symptoms are taken at face value, underlying causation and meanings are unexplored, and the patient's inner life is devalued or ignored. Thus, it is not inconceivable that a highly qualified psychiatrist with strong academic credentials and of good intention, could, as 'Adam' described, over a period of years and dozens of consultations fail to explore the client's inner thoughts and feelings and the critical family context.

At the 2013 APA meeting I had a conversation with a psychiatry resident from a mid-Western state, confirming Tasman's fears. The young man said his group of trainees had done mock vivas in preparation for their board exams. Their examiner asked one of his fellow trainees for the 'diagnostic formulation' for the patient she had seen. But none of the trainees knew what a 'diagnostic formulation' was. He said that having majored in chemistry for his pre-med degree he wondered if the tutor wanted to discuss medication and was referring to a chemical formulation. We had a fruitful discussion about the biopsychosocial model and comparisons between Australian and New Zealand versus US health care and psychiatry training. He was growing in awareness and hoping psychiatry in his state of the US could return to its former level of best practice.

9.4.1.3 **The bio-bio-bio model versus biopsychosocial reasoning**

There have been many critics of DSM-associated biomedical reductionism. Professor Michael First (Columbia University) has been deeply involved with the DSM verification process, as well as being critical of biomedical reductionism. In an article titled "Defining 'mental disorder' in DSM-V" co-authored with Professor Jerome Wakefield (School of Social Work, New York University), they stressed the importance of "dysfunction within the individual" as part of the concept of mental disorder, and that this dysfunction may still not be a biological dysfunction. They draw on a "worn but illuminating analogy from cognitive science" that "not

every software malfunction is a hardware malfunction" (First & Wakefield 2010, p. 1781). Thus:

> [T]here could be some disorders for which the dysfunction takes place at a psychological level of description involving the interaction of meanings. (p. 1781)

This echoes the psychoanalytic idea of neurosis, where for children and adolescents internalised conflicts and unresolved meanings and threats lead to emotional distress and oppositional behaviours. The level of dysfunction may be sufficient to warrant diagnoses such as separation-anxiety disorder, reactive-attachment disorder, ODD, other reactions to severe stress, and produce the symptoms of ADHD and ultradian cycling and irritability consistent with the PBD hypothesis.

First and Wakefield also caution that:

> [E]ven if a syndrome causes distress or impairment (i.e. criterion A and B are met), it would not be considered a disorder if it did not also indicate something that has gone wrong in the individual. (p. 1781)

In other words, emotional distress and behavioural impairment may be purely due to a stressful context. The case of 'Adam' shows how rapidly dysfunction can resolve when significant stressors are removed, as evidenced after he moved out of home.

Diagnosis is important, and the DSM and ICD classificatory manuals are a vital guide to researchers and clinicians. However, in addition to the above caveats, the manuals are inevitably unidimensional: they are closer to a "reliable descriptive nomenclature" than "valid classification of diseases" (Parry 2009b, p. 674; Appendix A9). The multiple perspectives that need to be considered in a diagnostic formulation were discussed in a day workshop at the 2009 APA annual meeting in San Francisco titled: "Going from the bio-bio-bio model forward to bio-psycho-social reasoning" (McHugh, Romanoski & Treisman 2009). The workshop was based on the book by the presenter, Professor Paul McHugh (John Hopkins University): *The Perspectives of Psychiatry*, these being: 'Disease, Dimension, Behaviour, Life Story' (McHugh & Slavney 1998).

McHugh and Slavney's model has substantial face validity. Humans are too complex for their problems to be understood by a merely descriptive psychiatry model. To illustrate this, I have

expanded below on McHugh's points, with reference to PBD. It is important to consider that the patient may have one or all of these perspectives involved in their presenting symptomatology:

- *Disease.* Dementia and other organic brain syndromes are clearly in the disease category, and Kraepelin's manic-depressive psychosis, or Bipolar-I disorder as it is now known, likely has an underlying neurophysiological dysfunction, a 'hardware' problem, that is amenable to treatment, for example with lithium. Reading the PBD literature and treatment guidelines it becomes apparent this is where the PBD children have been placed.
- *Dimension.* ADHD and milder cases of ASD appear to have aspects of dimensionality, where the boundary between normality and illness/dysfunction is blurred. For example, in cases of ADHD (apart from those with early neurodevelopmental damage such as lead poisoning or Foetal Alcohol Syndrome) the dimensional traits of distractibility-attentional focus, impulsivity-inhibition, and hyperactivity-hypoactivity are distributed in a roughly Gaussian normal distribution (Martin et al. 2014), similar to height. As multiple sources showed, including: the 1998 *JAACAP* debate (Biederman, 1998a. 1998b; Klein RG, Pine & Klein 1998a, 1998b); the results of the FCAP of the RANZCP survey (Parry, Furber & Allison 2009a); a similar German survey (Meyer, TD, Kossmann-Bohm & Schlottke 2004); the clinical vignettes comparison of UK and US child psychiatrist diagnosing practices (Dubicka et al. 2008); Kaplan's book and blog (Kaplan 2011b; Kaplan 2013); the comparisons of international diagnosis rates (Chapter 4.8.6.14); and the geographic divergence of academic perspectives (Chapter 7; Parry, Allison & Bastiampillai 2019b) – many children diagnosed with PBD in the US would be given an ADHD diagnosis in other jurisdictions or by US child psychiatrists sceptical of the PBD hypothesis. This implies the question of where to draw a pathology-versus-normality line on what amounts to temperamental traits then becomes a sociocultural issue.
- *Behaviour.* Addictions can be seen as having a strong behaviourist input of positive and negative reinforcers, but this also occurs for behaviours within family systems which contributes to the relative success of parent training for childhood behavioural problems. Such parent-child relational problems can be extreme and could well be the

basis for many a PBD diagnosis. 'Adam's' triggering interaction patterns with his mother illustrate this relational context.

- *Life story.* The life story narrative is a therapeutic engagement that brings the therapist and patient closer to the true self. A vast literature from psychoanalysis, self-psychology and narrative therapy attest to the value of life story work and re-authoring past traumas. For 'Adam' later psychotherapy at a trauma clinic helped him gain insight into the family dynamics at root of his problems and deprogram from the labelling effects of the PBD misdiagnosis. Parent-child dyadic therapies (Amos, Segal & Cantor 2015; Chambers et al. 2006; Becker-Weidman & Hughes 2008; Allen, B, Timmer & Urquiza 2014) show great promise in cases of children and parents with histories of intergenerational trauma. These include cases where the parents may have their own trauma related borderline personality disorder diagnosis or, in line with contemporary fashion, a bipolar spectrum diagnosis and the children have patterns of emotional and behavioural dysregulation that would meet several DSM or ICD diagnostic labels and, where it is used, the diagnosis of PBD.

McHugh and Slavney's approach is a more thorough multi-axial approach than the DSM allows, but it is important to take the further step and integrate these four approaches and "cogently integrate ... descriptive, biological, psychoanalytic, social, interpersonal, and behavioural approaches" (Hirschfeld 1994, p. 306).

Hirschfeld was describing the holistic approach in an obituary of Gerald Klerman, a key researcher in the psychobiology of depression at the NIMH. Klerman had coined the term 'neo-Kraepelinians' to describe the descriptive biomedical focus of his contemporaries, Robins, Guze, Winokur and Spitzer, who championed the descriptive psychiatry model of DSM-III.

It has been argued that the narrow focus on the descriptive and biological approaches by the neo-Kraepelinians, through over-reach beyond the disease model, led psychiatry over recent decades into what has been called an era of 'mindless psychiatry'.

9.4.1.4 **'Mindless' versus 'brainless' psychiatry**

In his 2005 presidential address to the RANZCP, Professor Philip Boyce (University of Sydney) referred to a "dumbing down" of psychiatry by using the DSM for simplistic "cookbook" diagnoses (Boyce 2006, p. 4). He criticised the "deification of the DSM" and stated:

> DSM has moved to become more than a manual, assuming the status of a holy document …
>
> The DSM approach is exemplified by … treating DSM disorders rather than individuals, typifying the simplistic approach; administer a structured diagnostic instrument, come up with a DSM diagnosis to look in the manual for the current vogue in pharmacotherapy for that diagnosis, and apply it. (p. 5)

This criticism could well be applied to the labelling and treatment of children and teens with PBD in research and clinical practice.

As Silove suggested, such misapplication of psychiatric nosology can be equated to 'biologism'. An equivalent expression would be 'mindless psychiatry', a term attributed to the eminent late US child psychiatrist, Professor Leon Eisenberg, (John Hopkins University; Harvard University). Early in his career Eisenberg conducted the first randomised control trial of stimulants for ADHD in adolescents and was a critic of the dominance and over-application of psychoanalysis, which he later called a period of 'brainless psychiatry' (Eisenberg 1986). Eisenberg's 1986 article in the *British Journal of Psychiatry* was titled "Mindlessness and brainlessness in psychiatry" and encompassed the large pendulum swing of opinion and practice he witnessed during his career. A posthumously published article titled "Were we asleep at the switch? A personal reminiscence of psychiatry from 1940 to 2010" (Eisenberg & Guttmacher 2010) attributed most of the problems of US health care and psychiatry to the "monetarization of medicine" (p. 89). He criticised the switch from 'mind' to 'body' and, reiterating his 1986 comments, said psychiatrists had:

> [F]or so long been pilloried by our medical and surgical colleagues as witchdoctors and wooly minded thinkers that many of us now seek professional respectability by adhering to a reductionistic model of mental disorder. We have traded the one-sidedness of the brainless psychiatry of the first half of the 20th century for a mindless psychiatry of the second half. (p. 93)

Lipowski used the same terms in his 1988 presidential address to the Canadian Psychiatric Association, titled "Psychiatry: Mindless or brainless, both or neither," where he strongly advocated for the biopsychosocial model despite its imperfections as a safeguard to good practice (Lipowski 1989).

So what contributed to the prevailing paradigm in psychiatry pendulum swing from a brainless to a mindless pole in the mid to late 20th century, that inadvertently facilitated the development of the PBD epidemic? A closer look at the social history of the DSM can shed some light.

9.4.1.5 **DSM, informational reductionism and reification**

> *Not everything that counts can be counted, and not everything that can be counted, counts.*
>
> William Bruce Cameron (1963, p. 13)

9.4.1.5.1 **The DSM as a 'monetarised' social process**

The overlapping syndromes and symptom clusters in psychiatry, and lack of recourse to laboratory confirmation, mean that defining diagnostic boundaries is still a matter of debate by committees. Whilst psychiatry as a profession, both in the US with DSM and globally with the ICD manuals, strives for evidence-based scientific rigour, the limited state of neuroscience curtails these scientific aspirations.

In his final editorial, Eisenberg allegorised the DSM process of deciding diagnostic boundaries as being akin to baseball umpires ruling on 'balls' and 'strikes':

> The new diagnostic scheme is a major advance over DSM-I and II. But with each iteration it becomes more fragmented and bureaucratized. It has become an industry—and a profitable one at that—for the American Psychiatric Association which makes tens of millions of dollars with each new edition because a DSM-IV code is the precondition for reimbursement. The situation has begun to resemble the debate among three umpires about the meaning of balls and strikes in the great American game of baseball. The first, a modest man, claimed only: 'I calls 'em as I sees 'em.' The second, an arrogant and officious man, insisted: 'I calls 'em as they is!' The third, Bill Klem, a man of philosophic bent, dismissed their

> comments with: 'They may be balls, they may be strikes, but they ain't nothin' until I call 'em!'. (Eisenberg & Guttmacher 2010, p. 93)

This arbitrariness of the DSM process is further illuminated and critiqued in two books that coincided with the publication of the DSM-5: (1) *The Intelligent Clinician's Guide to the DSM-5* by Canadian Professor Joel Paris from McGill University (Paris 2015); and (2) *The Book of Woe: The DSM and the Unmaking of Psychiatry* by psychotherapist Garry Greenberg (Greenberg 2013). Both books provide insight into the politics of DSM diagnostic working groups, study groups and committees. Both devote full chapters strongly critiquing the PBD phenomenon and the mixed blessing of the new disorder, DMDD, to combat the PBD epidemic.

Greenberg (2013) described the rise of PBD as being particularly driven by the MGH-Harvard group and the interest of the pharmaceutical industry in sponsoring this development. Interviews with members highlighted the social processes and debates within the APA's DSM committees to bring in TDD to counter the PBD epidemic. It was possible to view TDD as giving the impression of pathologizing temper tantrums, a potential source of embarrassment for the APA, and it was also possible some clinicians would ignore it and still resort to PBD diagnoses because, according to Shaffer on the committee, "the BD diagnosis justifies access to a higher level of resources" (p. 151). Some argued to instead make TDD a specifier to ODD for children with rages. However, that would still not circumvent the PBD diagnosing as ODD had a "stigmatized name" and was poorly reimbursed (p. 148). By defining DMDD as a mood disorder, these problems were solved. Greenberg noted:

> Parents might hesitate to ply their kids with stimulants and antipsychotics if they believe that they are merely calming them down, rather than treating their ADHD or BD (or, once the DSM-5 goes into effect, their DMDD). (p.353)

The DSM criteria now are seemingly arrived at in a milieu of 'monetised' medicine. As suggested in a previous article:

> Pharmaceutical companies are keen to use the DSM criteria to maximize profits. The more numerous the diagnoses and the broader the criteria, the greater the scope for pharmaceutical companies (and others) to exploit them. (Raven & Parry 2012, p. 512; Appendix A24)

Greenberg's insight into the internal workings of the DSM committees revealed a creation-of-disorder-category process based on the unique peculiarities of the US health system. It was hoped the 'invention' of DMDD would stem the prescribing of atypical antipsychotics. Given the data (Chapter 9.2.2) for atypical antipsychotic use in sedating aggressive boys, Paris pessimistically opined:

> No one would be surprised if children with DMDD routinely receive antipsychotics. … Child psychiatry, once noted for its [attention to] family life and social issues, has become focused on biological mechanisms and pharmacological solutions. (p.109)

More recently, Malhi and Bell (2019) stated in an article titled "Fake views: DMDD indeed!" that:

> DMDD has failed to fulfil the primary role of any diagnostic entity, that is, to inform treatment. Furthermore, the overdiagnosis of paediatric BD, the issue which led to the development of DMDD in the first place, has not been resolved by the introduction of this new diagnostic category ... urgent consideration should be given to expunging DMDD from DSM. (p. 710)

Malhi and Bell indicted that ICD-11 will not incorporate DMDD into its lexicon but a specifier of chronic irritability shall be added as a subtype of ODD. The authors also argued that DMDD had failed to stem the overprescribing to young children.

Both Boyce and Eisenberg note the shift that allowed for reification and medicalisation of behavioural problems taken out of context occurred with the third edition, DSM-III, in 1980. DSM-III was no longer a diagnostic guide developed in a professional milieu that recognised the complexity of psychopathological presentations, but represented a more definitive project that reified the constructs into allegedly discrete diagnostic biological entities.

9.4.1.5.2 **The DSM-III in context**

The political history of psychiatry that led to the new DSM-III in 1980 helps explain why psychiatric nosology became decontextualized. Broadly speaking psychiatric nosology can be viewed as a struggle between two different perspectives, embodied in firstly, Emil Kraepelin's more 'medical model' of categorisation by symptoms and course of illness, and secondly, the

'psychobiological' model of Adolph Meyer who advocated that psychiatric interviews should start with a developmental history and the context of the patient's life.

Engel's biopsychosocial model (Engel 1977) was widely discussed and adopted into medical school curricula during the ensuing years, such that a merger or at least a truce seemed to have occurred. The APA was under pressure on one side from government and the insurance industry who wanted to know exactly what they were paying for, and from the antipsychiatry movement and family systems theorists on the other, with their accusations that psychiatric diagnoses were only social constructs lacking in ontological reality. However, as Wilson (1993) described, social and economic pressures were increasingly impinging upon the APA. The DSM-II and preceding DSM-I and the mental disorders sections of the ICD-8 and ICD-9 were criticised for lacking clarity. These manuals made frequent references to 'reactive states' and 'neurosis' that begged the question of context. Diagnoses were to a great extent in the eye of the beholding clinician.

This was highlighted at the time by the geographical variation in the diagnosis of schizophrenia between the US and Europe. US psychiatry dominated by psychoanalysis, was overdiagnosing schizophrenia partly based on the subjective experience of the therapist, the "praecox feeling" (Parnas 2011). Although there may be some validity in the intersubjective deficit of empathy in engaging someone with a schizophrenic psychosis (Grube 2006), such subjectivity could also lead to over-confidence in the clinician. Perhaps this is a similar issue to what Biederman meant when he said he was able to see the irritability of PBD as "qualitatively distinct" to other instances of irritability (Chapter 4.8.2.23) and Papolos as "the view – if you have the view you get it" (Chapter 4.6.6) in being able to diagnose PBD.

Based on the emerging need for a more objective and reliable classificatory system, DSM-III adopted a nomothetic, 'neo-Kraepelinian' model, based on symptom criteria check-lists. Simultaneously jettisoned was the 'Meyerian' ideographic model, that viewed psychiatric syndromes as arising out of individual lives with multiple interactive biopsychosocial causations (Double 1990).

The DSM-III descriptive psychiatry model thus required a degree of informational reductionism. The psychoanalytic quest for meaning behind the symptoms was lost,

something that Wilson (1993) noted in an article titled “DSM-III and the transformation of American psychiatry: A history”. This was previously the goal championed by psychiatrists like Karl Menninger. Wilson highlighted the growing power of the biological psychiatry lobby, quoting Akiskal who said the previously dominant “psychosocial model” was “soft-headed pseudopsychiatry” and the DSM-III task force stating they saw their role as “defence of the medical model” (p. 405).

Wittgenstein (1953) proposed that language and concepts affect perception: that is, what is in our vocabulary we see; what is not can easily remain invisible. Thus, what is omitted from a diagnostic manual is as critical as what is added. A sociologist with a long career studying psychiatry, Professor Andrew Scull (UC San Diego), commented on DSM-III, suggesting the “revolution” in psychiatry’s paradigm came in the form of an:

> [A]nti-intellectual system published in book form: a checklist approach to psychiatric diagnosis and treatment … with scant regard for whether the new labels … cut nature at the joints. (Scull 2010, p. 1247)

Medical journalist Christopher Lane interviewed committee members from the DSM-III Task Force, including the chair Robert Spitzer who admitted that the task force decided the term “neurosis” had to be “eliminated” because of its “psychoanalytic meaning” (p. 50). Lane concluded that a political agenda to depose psychoanalysis from its perch atop US psychiatry’s power structure drove the atheoretical model of DSM-III (Lane 2007, p. 61)

With reference to context and internalised psychological conflicts expunged from the manual, it became easier for symptoms reflective of reactive psychosocial processes to be reified to neuropathological entities, and as Paris (2015) states, child psychiatry came to see “… almost every symptom as a reflection of abnormal mood.” (p. 110)

This change in psychiatry’s culture that DSM-III contributed to, possibly explains the perspective of Professor Biederman towards attachment theory when I asked why his research didn’t incorporate instruments for assessing secure and insecure attachment with his research cohorts, at the 2012 IACAPAP World Congress. He replied with these three exact sentences: “Attachment theory is just that, a theory.” “It is philosophy.” “We are researching science.”

9.4.1.5.3 **Decontextualised psychiatry**

'Adam' said: "there was a lot the psychiatrist should have asked about" (Parry 2014a, p. 339). Psychiatric symptoms do not occur in a vacuum; neither do most medical symptoms either for that matter. Again, in 'Adam's' words, "there is always context" (p. 339).

Greater reliability of syndrome description does not necessarily mean greater validity of diagnosis. Similar symptomatic presentations can have differing causation in different individuals. The introductions in the DSM-III and DSM-IV manuals specifically warn against reification of diagnoses, and that the DSM must "not be used in a cookbook fashion" (DSM-IV, APA 1994, p. xxiii). Unfortunately, introductions to manuals like the DSM are rarely read.

'Adam' is not alone in having suffered from misdiagnosis and diagnosis without consideration of context. The recent publication of DSM-5 occurred amidst significant controversy and protest. Recognizing a widespread problem, thousands of mental health clinicians and over fifty mental health organizations signed an online open letter protesting the decontextualized nature of the DSM (CDR 2011). The open letter quoted from a statement by the British Psychological Society:

> [Taxonomic] systems such as this [DSM-5] are based on identifying problems as located within individuals. This misses the relational context of problems and the undeniable social causation of many such problems. (BPS 2011).

There are many 'Adams' and their families affected by simplistic symptom-based diagnostic practice. Spitzer, who had emphasised the nomothetic over the ideographic in psychiatric nosology, revised his viewpoint late in life. In a foreword to *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow into Major Depressive Disorder* (Horowitz & Wakefield 2007), Spitzer stated:

> [This book] has forced me to rethink my own position … The very success of the DSM and its descriptive criteria … has allowed psychiatry to ignore basic conceptual issues … especially the question of how to distinguish disorder from normal suffering … DSM diagnostic criteria … ignored any reference to the context in which they developed.

As ‘Adam’ recounted (Parry 2014a; Appendix A26), he and his family experienced a high degree of suffering. It may have been intense and beyond the norm for healthier families, but the suffering was embedded in intergenerational family dynamics. Now in their mid to late twenties ‘Adam’ and his siblings have gained insight into these dynamics. That insight has been liberating for them.

Is it reasonable to conclude that a predisposing cause of ‘Adam’s misdiagnosis as having bipolar disorder was this paradigm shift in psychiatry to a biomedical model? It would seem unarguable that ‘biologism’ was one of the influences on ‘Adam’s psychiatrists that led them to misconstrue parent-child conflict as mania, prescribe him up to eight psychotropics concurrently and misdiagnose polypharmacy side-effects as a hypothesised mitochondrial disorder involving months of high-tech investigations.

In addition to being a method of inquiry, science involves a social process. Scientific disciplines do not build on knowledge in a purely linear fashion, but at times undergo dramatic paradigm shifts (Kuhn 1962). The dominant paradigm governs what is acceptable to study, research, publish and practice. Softer sciences like psychiatry can possibly be more susceptible to paradigm shifts. However, psychiatry is not just an ‘academic’ discipline: what is emphasised in teaching and research plays out in practice, with real life consequences, as ‘Adam’ described well.

Bracken et al. (2012) described the dominant paradigm in psychiatry as a “technological paradigm” that has relegated relationships, meanings and values to secondary concerns and instead focused on symptomatology and interventions “independent of context” (p. 430). They argued psychiatry must break free from the constraints of this technological paradigm:

> Psychiatry is not neurology, it is not a medicine of the brain. Although mental health problems undoubtedly have a biological dimension, in their very nature they reach beyond the brain to involve social, cultural and psychological dimensions. These cannot always be grasped through the epistemology of biomedicine. (p. 432)

9.4.1.5.4 PBD: emblematic diagnosis for decontextualisation

The head of the DSM-IV committee, Allen Frances, was highly critical of the DSM-5 process as illustrated in his book: *Saving Normal: An insider's revolt against out-of-control psychiatric diagnosis, DSM-5, Big Pharma and the medicalization of ordinary life* (Frances 2013). He was scathingly critical of PBD in his regular article in *Psychiatric Times* (Frances 2010b; Chapter 4.8.2.24). Although Frances noted that strict adherence to DSM-IV criteria would have ruled out PBD, the nomothetic and by default biomedical model of DSM-IV allowed PBD to flourish within the Bipolar-NOS category. In a recent article Frances and colleagues (Batstra et al. 2012) went further in criticising the nomothetic medical model:

> A classic criticism against medicalization applies: the 'medical gaze' locates the problem and the place of treatment within the individual child, and neglects possible social dimensions of the problem. (p. 493)

As demonstrated in Chapter 8, the PBD literature is nearly devoid of serious consideration of contextual factors. The methodology in such research leans heavily on structured parent interviews: as in research, so in clinical practice. For 'Adam' the sessions with his psychiatrist involved his mother and the psychiatrist discussing his symptoms with little space for him to ever talk about the abuse by his brother or the conflict with his mother.

It can be argued that the post-DSM-III adherence to descriptive symptom-based diagnoses is an issue as much as the reified PBD hypothesis. DSM-5 introduced DMDD with the primary rationale of curbing the diagnosis of PBD. However, it is questionable whether this new diagnosis, if applied in 'Adam's case, would have led to any appreciable alteration in treatment. DMDD still embodied the same decontextualized model.

9.4.1.5.5 The "Power-Threat-Meaning Framework" for recontextualized nosology

As mentioned in the Introduction, the British Psychological Society has recently put forward an alternative framework to the DSM's symptom checklist approach, for understanding mental distress and apparently abnormal behaviour. It is named the "Power-Threat-Meaning Framework" (Johnstone & Boyle, 2018) and was subtitled: "Towards the identification of patterns in emotional distress, unusual experiences and troubled or troubling behaviour, as an alternative to functional psychiatric diagnosis". The framework is described in a 414 page

e-book and draws upon a vast bibliography with contributions by many of the UK's leading academic psychologists.

Whereas the biopsychosocial model rather simply reminds us to look broadly and not be too reductionist, the Power-Threat-Meaning Framework informs us what patterns to be on the lookout for. The framework notes that the problem with the 'DSM-mindset' is it is based on a mechanistic bodily symptom approach that fails to properly account for the subjective and meaning-making activity of human minds or 'selves' that create thoughts, emotions and behaviours. The framework emphasises that these patterns of distress occur in the midst of social and cultural discourses about acceptable and unacceptable modes of expression. It also emphasises the role of stress/adversity on multiple contextual levels – biological, psychological, social, cultural, ideological and mediation of patterns via cognitive style, temperament, belief systems etc. and while everything is mediated via a biological brain, a biomedical reductionist view cannot capture or understand the interactions and pathways to presenting patterns of symptoms for any individual self.

In terms of expressions and experience of distress and troubling behaviour (the kind of 'symptoms' that led 100,000s of children to be misdiagnosed with PBD), the Power-Threat-Meaning Framework would highlight the "coping and survival mechanisms which may be more or less functional as an adaptation to particular conflicts and adversities in both the past and present" and assign a "central role to personal agency" in the creation of such patterns of distress and behaviour (Johnstone & Boyle, 2018; p. 8). The framework is neatly summarised in the following passage:

> [T]his framework for the origins and maintenance of distress replaces the question at the heart of medicalisation, 'What is wrong with you?' with four others:
>
> - 'What has happened to you?' (How has Power operated in your life?)
> - 'How did it affect you?' (What kind of Threats does this pose?)
> - 'What sense did you make of it?' (What is the Meaning of these situations and experiences to you?)
> - 'What did you have to do to survive?' (What kinds of Threat Response are you using?)

The authors clarify that this does not mean that regular patterns correlating to DSM categories don't exist, but:

> Rather, it implies that these regularities are not, as in medicine, fundamentally patterns in biology, but patterns of embodied, meaning-based threat responses to the negative operation of power (p. 9).

If we take this framework and apply it to 'Adam' in the context of his life's narrative (Parry, 2014a; Appendix A26), his threat responses become meaningful, clear and purposeful, not caused by some brain-based bipolar disorder. The case of 'Alicia' presented by Floersch et al. (2009; Chapter 9.2.3) also illustrates her threat responses triggered by the negative operation of power in her life (her beloved grandmother's death precipitating the family loss of grandparental home) and threat to her nuclear family resulting in her threat responses of oppositional outbursts and sibling rivalry. Responses that in turn threatened her mother were labelled as PBD due to a DSM diagnostic framework of medicalisation, rather than meaningful responses to loss and threat in her life narrative.

Further, the Power-Threat-Meaning Framework expands upon the basic instinctive sympathetic nervous system responses to threat as described in Chapter 2.5.3. These instinctive behaviours being the 'fight/flight/freeze/appease' threat responses that children choose, based upon their life experiences and sociocultural contexts. An over enthusiastic reductionistic DSM checklist approach might label such natural defences as Bipolar-NOS or 'ultradian cycling' or 'chronically irritable' PBD, or rebadge as ODD, CD, ADHD, ASD or DMDD. It is past time for the sake of children's welfare (as well as adolescents' and adults') to stop simply describing behaviour, but to go further and look for the meaning in the patterns of 'symptoms'.

9.4.1.5.6 Informational reductionism in PBD research

Anecdotal communication suggested it has been difficult at least until recent years for critics of PBD to publish in the US psychiatric literature (e.g. Prologue, p. 15; Chapter 4.8.2.13; Chapter 4.8.2.16). In an era where quantitative research appears to be held in higher regard than qualitative, it may be that contrary views about PBD are seen as opinion-based and

lacking data, reflecting a 'catch-22': those who dispute the construct validity of PBD are unlikely to have generated data on something they don't see as valid.

The extensive PBD research literature has reflected for the most part a biomedical reductionist and taxonomic approach to the phenomenology of children and teenagers' behaviour, where the emphasis has been on rating scales and quantitative data. The paediatric bipolar research literature shows high inter-rater reliability for questionnaire instruments, but it is basic science that reliability does not equate with validity. Einstein is reported to have chalked on a blackboard in his Princeton office Cameron's maxim: "Not everything that counts can be counted, and not everything that can be counted, counts" (Quote Investigator, 2010). Even in physics the quantitative approach is not everything. This is exemplified in the following examples. Biederman et al. (1995) used subscales of the Child Behaviour Checklist (CBCL) to define broad phenotype PBD or 'juvenile bipolar disorder' (JBD), hence the "CBCL-JBD". However, a 10-year follow-up of pre-pubertal children diagnosed by the CBCL-JBD was found to lack predictive validity into adolescence for bipolar disorder (Halperin et al. 2011). A diagnostic checklist from *The Bipolar Child* accessible online at www.jbrf.org was also found to lack predictive capacity for paediatric age range bipolar disorder (Rucklidge 2008). Such a narrow symptom-focused approach risks missing some of the most important factors of all, namely the contextual issues of child maltreatment, insecure and disorganised attachment, family/parenting stressors and trauma.

9.4.2 Neglect of attachment and developmental trauma

As the bibliometric review of the PBD literature revealed, the PBD literature mostly neglected attachment and developmental trauma factors (Chapter 8). This oversight can be considered as having occurred within the wider context of psychiatric nosology because, despite significant advances in the attachment theory and traumatology research literature, both DSM-III and subsequent editions have generally not incorporated this work (Dignam, Parry & Berk 2010; Appendix A12). There have been calls to address this deficiency. An editorial in the *American Journal of Psychiatry* stressed in its title that a major issue for DSM-5 was that of "Relational diagnosis: an essential component of biopsychosocial assessment" (Denton 2007). The editorial commenced with the statement:

> We are hardwired to seek out attachment, and relational processes will always be an essential part of the human experience (1). Although DSM strives to apply the biopsychosocial model, there is a notable and strikingly absent consideration of the role of relational processes and disorders in the development, maintenance, and manifestations of mental disorders. (p.1146)

Silberg and Dallam (2009), focusing on dissociation in children and its association with disorganized attachment, relational stress and trauma, note that "children with dissociative disorders are frequently misdiagnosed because of their comorbid symptomatology" and one factor is because "child-specific categories of dissociation do not exist in DSM-IV" (p. 70). The following examples provide evidence that this occurred.

It is concerning that Blader and Carlson (2007) found that a disproportionate number of Afro-American children received the PBD diagnosis. Further, Harris stated that many children she had worked with in the Boston inpatient unit diagnosed with PBD had attachment trauma histories and were in foster care. Harris also noted the overlap of neurodevelopmental delays related to abuse and trauma histories in the presentations of children given the PBD diagnosis (Harris, J 2005).

Levin, dealing with children in a residential program being treated with polypharmacy cocktails typically prescribed for a PBD diagnosis, found over a 2-year period that milligrams of psychotropic medications could be reduced by 80% while aggressive incident reports simultaneously fell by 100%. The reductions became possible by tapering medications while addressing trauma, attachment, milieu, and other factors. Complex developmental trauma or 'Developmental Trauma Disorder' (Cook, A et al. 2005; van der Kolk 2005) was seen to better describe their presentations (Levin 2009).

This is not to eschew the possibility of diagnoses that warrant pharmacotherapy and advocate for brainless psychiatry. Developmental trauma can precipitate those constitutionally vulnerable to psychotic disorders into manifesting full symptomatology (Read & Argyle 1999), but the effects of trauma can also present as affective instability and other ego defences that may superficially resemble psychotic or severe mood disorders. Dissociation as a defence against trauma can lead to symptoms easily confused with hypomanic and psychotic states (Silberg & Dallam 2009). Biomedical research has led to significant advances in understanding

brain development in the context of a child's attachment relationships and the effects of attachment disruption and trauma (Schore 2003; Teicher & Samson 2016). Attachment theory is a bedrock concept of child psychiatry and the wider field of developmental psychology, despite neglect of it in the PBD literature.

Herman-Lewis (1992) posited that society is biased against the acknowledgement of trauma:

> All the perpetrator asks is that the bystander do nothing. He appeals to the universal desire to see, hear, and speak no evil. The victim, on the contrary, asks the bystander to share the burden of pain. The victim demands action, engagement, and remembering. (p. 7)

However, further research finds that even the victim of intrafamilial child abuse is prone to minimize and/or deny such trauma due to a "social desirability bias" that supports individual self-esteem and the image of family cohesion (Church et al. 2017, p. 2). In Australia *The Royal Commission into Institutional Responses to Child Sexual Abuse* reported that child sexual abuse "thrives on cultures of silence and secrecy", driven by in this instance by religious institutions seeking to protect reputation (Wright & Swain 2018, p. 151). Wright and Swain's report was titled "speaking the unspeakable, naming the unnameable". Families with dysfunction and intergenerational trauma histories also are subject to a ubiquitous 'social desirability bias' with fear of both public shame and of the real consequences of child-protection service notification. For such families, speaking of intrafamilial abuse and trauma can be threatening on individual and family systemic levels. Therefore, given the community rate of child sexual abuse and physical abuse have been estimated at 7 – 13% and 10 – 25% respectively (May-Chahal & Cawson 2015; MacMillan et al. 1997; Pereda et al. 2009; Radford et al. 2013; Rosier 2017), then the tendency for parents to not report such data on structured clinical interviews or to treating clinicians is likely to be common.

Thus, nuclear families and sole parents, struggling in a modern world of complex stressors that offers minimal extended family, tribe, or village-like support, are likely to be attracted to simple biomedical explanations for disturbed childhood emotions and behaviours, that imply no blame or need for difficult changes to the modern family. There is also the allure of a quick biomedical fix for both families and clinicians, for whom writing a prescription may satisfy a desire for immediate action and assistance.

However, neuroimaging of children with disorganized attachment and trauma histories has revealed impaired right prefrontal cortex control over a hyperactive right amygdala (Schore 2002; Tieghem & Tottenham 2018). The authors suggest this can be explained in terms of the function of these structures in attachment relationships and for survival in the face of threat. Neuroimaging of children diagnosed with PBD (Pavuluri et al. 2009; Pavuluri 2009; DelBello 2009) gave essentially the same findings but researchers made no reference to attachment and trauma factors. In response to questions at the 2009 AACAP annual meeting, both Pavuluri and DelBello in each of their neuroimaging presentations conceded that PTSD had not been investigated in their cohorts (Chapter 4.8.2.20).

The potential role of the DSM cannot be overlooked here: The most recent edition, DSM-5 (APA 2013b), modified the criteria for PTSD in the case of children aged 6-years-old or younger. The new criteria incorporate consideration of children witnessing domestic violence or learning a parent has been exposed to trauma as an 'A criterion' for trauma exposure. They also include as 'D criteria' "negative emotional states" and "socially withdrawn behaviour", and as 'E criteria' "irritable behaviour and angry outbursts (including extreme temper tantrums" (APA 2013a, p. 148). Recognising such symptoms in the context of family-related trauma could prompt research similar to the neuroimaging studies of DelBello (2009) and Pavuluri (2009) where PTSD is included in at least very young children as a diagnosis option.

Nonetheless, the expansion of PTSD for family-related trauma for under-7-year-olds was not extended to older children and adolescents, nor did it incorporate more subtle but vitally important attachment relationships. Secure attachment with a caregiver can provide a protective buffer to the effects of childhood trauma, whereas insecure attachments can lead to increased vulnerability (Ludy-Dobson & Perry 2010). Further, Developmental Trauma Disorder, since it specifically deals with attachment issues, could be proposed as a more accurate descriptor for many children diagnosed with PBD (Levin 2009). However, Developmental Trauma Disorder is not yet officially within the DSM. This, as well as the late addition of early childhood PTSD to the DSM, may help explain why ADHD and PBD received consideration in the PBD neuroimaging research, but not so Developmental Trauma Disorder and attachment and contextual factors.

9.4.3 **Shrinking boundaries of normality**

Beyond the tendency to deny and avoid the realities of child abuse, there are signs of an increasing narrowing of the bounds of what is considered normal childhood behaviour. An article in *The New York Times* titled "Still in a crib, yet being given antipsychotics" (Schwarz 2015), reported that "at least 10,000 children age 2 or 3" were diagnosed with ADHD and prescribed stimulants with a similar number of US toddlers prescribed antipsychotics and antidepressants. The article quoted Ed Tronick, a professor of developmental and brain sciences at the University of Massachusetts Boston:

> "There's this very narrow range of what people think the prototype child should look like. Deviations from that lead them to seek out interventions like these. I think it's just nuts." (para. 15)

In a chapter titled "America's intolerance of diversity in children's performance and behaviour," within his book *The Last Normal Child,* Diller (2006) noted the changing attribution of causation in US society. Traditionally, children's behaviour was understood in moral terms, the child being considered to have self-agency unless obviously intellectually impaired. Problematic behaviour was seen as 'lazy' or 'bad'. By the 1950s psychoanalytic concepts of childhood and parenting became known to the US middle classes through books such as those of paediatrician Dr Benjamin Spock, encouraging more affectionate and permissive parenting, although a 'good spanking' was still the working-class norm. These concepts promoted an apparent shift from blaming parents and mothers from not being strict enough, to being too strict. Diller went on to note that the influence of the DSM-III in 1980, along with pharmaceutical company influences on medical research and CME, Kramer's 1993 book *Listening to Prozac* and the idea of 'cosmetic psychopharmacology', together ushered in the current era of blaming the child's physiological brain. From this flowed the idea of 'chemical imbalance', which in turn mandated a pharmacological fix.

Accompanying this medicalisation of problematic but otherwise normal behaviour, has been the extension downwards of high educational expectations to younger age grades, such that "preschools prepare the children of the middle and upper-middle class for the rigors of kindergarten" (p. 10). Diller states:

> The demands on children's educational performance and behavior in school have vastly increased over the past twenty-five years. I shake my head in uneasy wonderment when I compare what pediatricians considered "normal" development for a five-year-old in 1980 with pediatricians' performance expectations for five-year-olds today. (p. 10)

Reading Diller's book, and his description of US educational expectations, it seemed sadly familiar to education and paediatric/child psychiatric practice regarding ADHD here in Australia. Fortunately, one country at least does things differently. Finland regularly tops global comparisons in educational outcome, such as the "PISA" (Programme for International Student Assessment) score, based on a school system that has only public comprehensive schools where all sectors of society are stakeholders (OECD 2011). According the Butler (2016) Finnish schools initially provide play-based learning and only start academic classwork at age 7, eschew standardised testing, give teachers immense autonomy over curricula and assessments, limit classroom hours and give minimal or no homework. As Finnish education authorities stated in the documentary *Where to Invade next: prepare to be liberated* (2015), this is all on the basis that "children need to be children first".

In comparison, in Australia academic classwork begins by 5-years of age and young children are subjected to annual national examinations of literacy and numeracy skills upon which they and their schools are graded. These exams are a known source of anxiety for students and teachers. In this stressful school environment extra-funding for classroom behaviour support has been linked to an ASD diagnosis creating diagnostic upcoding pressures for ASD. Schools request 'verification forms' signed by child psychiatrists and paediatricians to indicate that children have ASD (Basu & Parry 2013; Appendix A25). Diller suggests a similar need by schools drove the initial ADHD epidemic in the US. Although this was not directly the case for PBD, this now globally widespread ethos of 'blaming the child's brain' is inherent in this practice and is the milieu into which the PBD hypothesis came in the mid-1990s. While schools may have pushed for upcoding to ADHD in the US, and for ASD in Australia, the US health system may have mainly driven diagnostic upcoding to PBD in the US.

9.4.4 **Diagnostic upcoding in the US health system**

Between 1990 and 2000, there was a marked reduction in length of stay for child and adolescent psychiatric inpatients with only a slight increase in number of admissions in US community hospitals (Case et al. 2007). More severe diagnoses were given in 2000 than in 1990. The authors noted:

> Under scrutiny of managed care review, inpatient providers may be indicating more serious diagnoses to justify admission or secure greater reimbursement, a process a process termed *diagnostic upcoding.* (p. 95)

The diagnosis of bipolar disorder had increased the most, from 2.9% in 1990 of all mental health discharge diagnoses to 15.1% in 2000, while the diagnosis of adjustment disorders fell from 14.3% to 5.6% and primary substance use disorders fell from 16.8% to 4.8%.

Harrison, Cluxton-Keller and Gross (2012) described inadequate access to non-drug therapy services:

> Many evidence-based, behavioral, non-pharmacological treatments are now available for children with emotional and behavioral disorders. However … Parent training and cognitive-behavioral therapies can be costly for families without adequate insurance and may seem too time-consuming for families in desperate need of a "quick fix." Under these circumstances, medication may be seen as an effective, affordable alternative. (p. 4)

Personal communication with several US colleagues at the 2009 AACAP annual meeting in Hawaii, US, at the poster presentation of the FCAP of RANZCP PBD survey results (Appendix A6), described the phenomenon of diagnostic upcoding to PBD. One child psychiatrist said it varies between insurance companies but typically she had to phone the insurer within the first 15 minutes of the first consultation. She would then be asked by a clerk as to what the diagnosis is. If she says she doesn't yet have a diagnosis the clerk will reply that they cannot reimburse the session, if she says it is a 'parent-child relational problem' (V-code diagnosis in DSM-IV) then she will be told that is not reimbursable, if she says 'adjustment disorder' she may be told she will be reimbursed for a couple of sessions, if she says 'bipolar disorder' then she will be allowed to see the child and family for ongoing sessions. Other US colleagues

bemoaned the fact that many employers directed them to do '15-minute med checks' and that they were forced into a narrow medication focus in their work.

In a section titled "Managed Care and Diagnostic Distortions", Kutchins and Kirk (1997) confirm the observations of this US child psychiatrist, describing US psychiatric practice:

> In countless clinics, private practices, and supervisory sessions, the game is how to fit a diagnosis to the presumed preferences of a managed care corporation and its faceless bureaucrats not to the client's mental disorder. (p. 257)

Kutchins and Kirk (1997) then described a case history of a 7-year-old girl labelled with oppositional-defiant disorder (ODD) residing in a "chaotic", extremely stressful home environment. The mental health worker found the girl to relate normally in play therapy and concluded her behaviour was "adaptive" to her home environment, yet noted "the clinical diagnostic and treatment procedures ... follow a model of individual pathology or disorder ... disregarding family or systemic function in favour of pathologizing the child" (p. 259).

Inequities in the US health care system, and contentious efforts at reform such as 'Obamacare' continue to be a global news item and have been exposed in documentaries such as *Sicko* (2007). At the time of writing, US Senator Bernie Sanders (Independent, VT) had sponsored a bill titled 'Medicare for All' to the US Congress for a universal payer system (Gambino 2017). These problems persist despite or due to, as Eisenberg and Guttmacher (2010) described, the "monetarization of health care" (p. 98) that sees the US expend over 16% of GDP, the majority in the private sector on health, while the OECD average is just under 9% of GDP of which over two thirds is in the public sector (Figure 9.2). Of the 35 OECD countries, only the US and Greece have significantly less than universal health coverage (Figure 9.3) (OECD 2015).

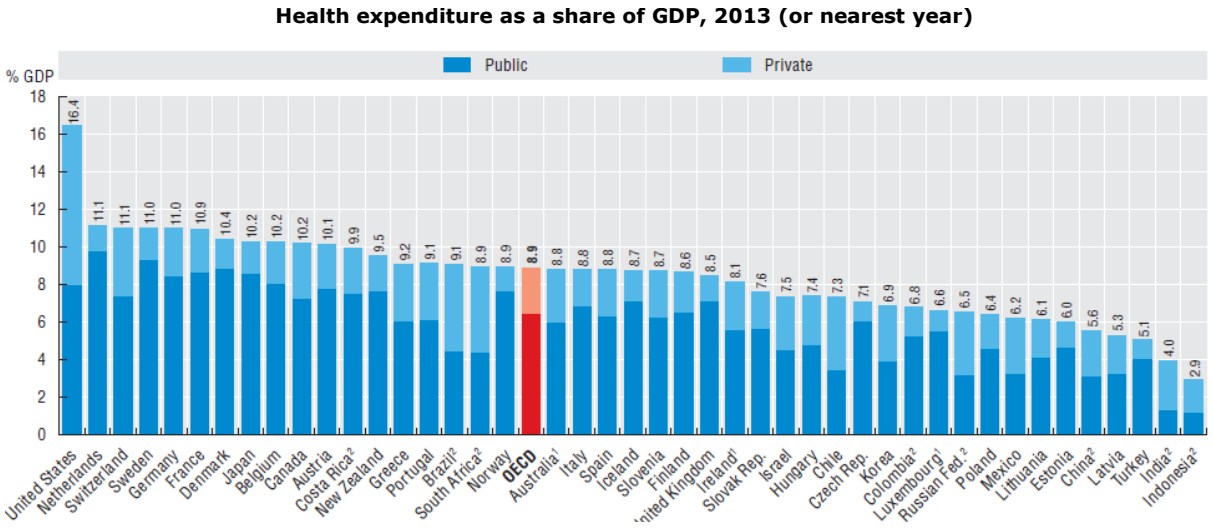


Figure 9.2: Health expenditure as a share of GDP, 2013 (or nearest year) (OECD 2015, p. 167). Reproduced with permission.

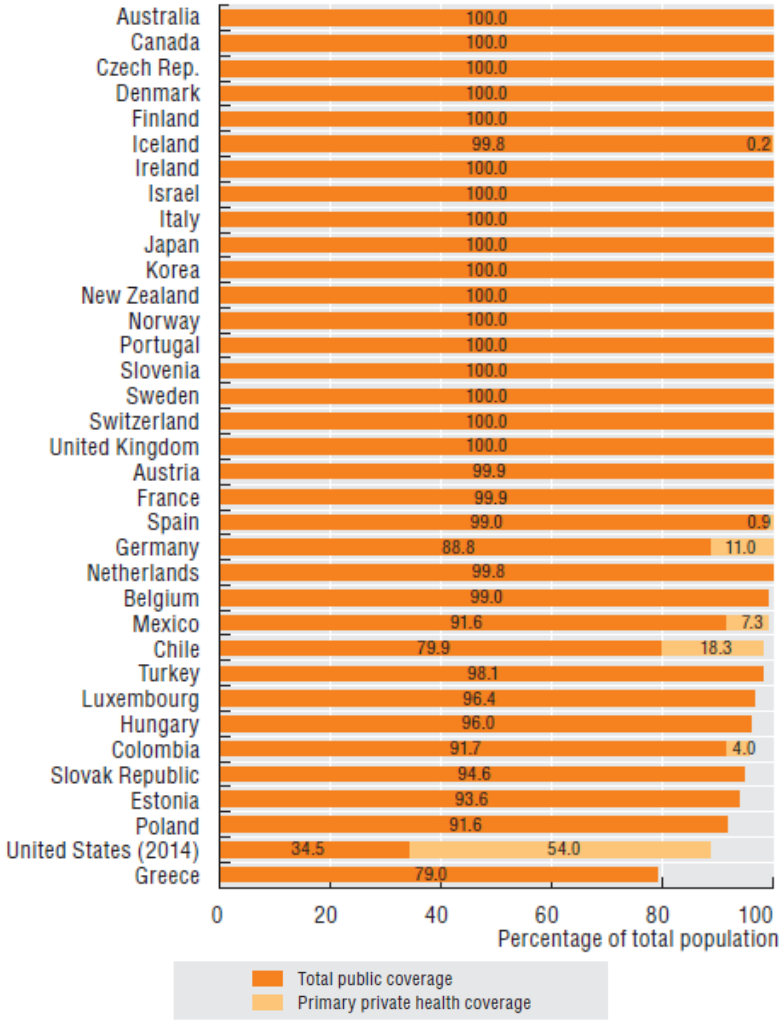


Figure 9.3: Health insurance coverage for a core set of services, 2013 (OECD 2015, p. 121). Reproduced with permission.

Former APA president Harold Eist (1999) enunciated the unethical consequences of this managed care model for the citizens of the US:

> "Corpricare" has created great distress and demoralisation in the community of psychiatric healers to the huge detriment of the public and profession with their insensitive and uncaring attack on medical ethics. Take ethics and compassion out of health care and what is left is a cruel jungle where the sick … are easy prey for financial exploitation. (p. 7)

In 2007, it was reported that 79 million adults in the US had problems paying medical bill debts (Commonwealth Fund 2008). In 2010 the CEO of the health insurer Aetna was compensated $68 million for less than a year's work (Strauss 2011). By 2017 the CEOs of the 11 largest health insurance companies received a combined annual income of $342 million, the largest compensation package being $83 million (Sweeney & Stankiewicz 2018). These sums are eclipsed by the remuneration to pharmaceutical industry executives, with the CEO of Gilead Sciences reported recently as a top earner with annual compensation of $900 million (Siegel & Columbus 2017).

Eist (1999) described the system as "Corpricare", caring for the profits of the private health industry (p. 4). These inequities combined with a rationing process based on DSM diagnostic category for access to services therefore appear as another driver of the PBD epidemic.

9.4.5 Influence of the pharmaceutical Industry

> *Researchers sign confidentiality agreements, and inconvenient data never see the light of day. The very categories within which we think about cognitive and emotional troubles are manipulated and transformed to match the requirements of the psychiatric marketplace.*
>
> Andrew Scull
>
> A psychiatric revolution.
>
> *THE LANCET* 10 April 2010, p. 1247

9.4.5.1 **Conflict of interest issues**

9.4.5.1.1 **AACAP, *JAACAP* and conflicts of interest with respect to SSRIs**

Apart from one notable exception (Biederman 1998a, 1998b; Klein RG, Pine & Klein 1998a, 1998b), it was somewhat mystifying that vigorous academic debate generally did not occur at AACAP conferences or within its flagship journal, *JAACAP*, before the PBD hypothesis was prematurely translated into widespread clinical practice. This history with AACAP and its journal appears to be a parallel of a previous debate regarding overemphasising benefits and minimising harms of the SSRIs in the paediatric and youth age group.

Many of the leadership within the Academy and the journal have extensive disclosure statements. How this might be relevant is illustrated in 'Study 329' of GSK's SSRI medication paroxetine for depression in adolescents (Keller et al. 2001). This study has been described as a fraudulent ghost-written study where data was managed so as to emphasise benefits and suppressed so as to minimise harms of the manufacturer's drug (Le Noury et al. 2015; Henry & Fitzpatrick 2015; Doshi 2015; Godlee 2015). Despite calls for *JAACAP* to retract the article (Jureidini & McHenry 2011; Doshi et al. 2013), the journal and AACAP itself have defended the study. The lead author of 'GSK Study 329', Professor Martin Keller (Brown University), is a lead investigator in the COBY study.

One of the many co-authors of Keller et al. (2001), was Professor Karen Wagner (University of Texas), who had six PBD related articles in the *Web of Science* citation tree search (Chapter 7). In a further example of conflicts of interest affecting published psychiatric literature, it has been revealed she gave her name to a ghost-written article in the *American Journal of Psychiatry* (Wagner et al. 2004). The article reported on a randomised controlled trial for Forest Laboratories' SSRI citalopram, in a paediatric depression cohort. Court subpoenaed documents reveal the article was pre-written and then Wagner was then sought out to be the lead author (Jureidini, Amsterdam & McHenry 2016). Wagner is, at the time of this thesis submission, president of AACAP.

The *Journal of Affective Disorders* under Akiskal's long chief-editorship, and *JAACAP* have the highest number of publications on PBD (Chapter 7). The majority of these articles have been almost completely favourable to the PBD hypothesis, with dissenting articles such as the 1998

debate of Klein RG, Pine and Klein (1998a, 1998b) vs Biederman (1998a, 1998b) and McClellan's commentary (McClellan 2005) to the 2005 PBD treatment guidelines (Kowatch et al. 2005), being two of the few exceptions until the stark trans-Atlantic comparison of bipolar diagnoses was published in 2014 (James et al. 2014).

It should be noted that many medical journals are to some degree financially dependent on pharmaceutical industry money, in part because the publication of a favourable drug trial means large income from companies purchasing reprints of such articles for sales-force distribution to doctors. In an article titled "Conflicted medical journals and the failure of trust, accountability in research", Jureidini and McHenry (2011) stated:

> Our experience with *The Journal of the American Academy of Child and Adolescent Psychiatry* (JAACAP) illustrates the nature of the problem. The now-infamous Study 329 of paroxetine in adolescent depression was negative for efficacy on all eight protocol-specified outcomes and positive for harm, but JAACAP published a report of this study that concluded that "paroxetine is generally well tolerated and effective for major depression in adolescents." The journal's editors not only failed to exercise critical judgment in accepting the article, but when shown evidence that the article misrepresented the science, refused either to convey this information to the medical community or to retract the article. (p. 45)

9.4.5.1.2 **The roles of KOLs**

Jureidini and McHenry (2009) in an article titled "Key Opinion Leaders and paediatric antidepressant overprescribing", linked the following factors to the "misleading influence" of KOLs: publication bias, editorial passing over of poor methodology, selective reporting of drug trial data and unjustified conclusions frequently published in journals. They noted:

> Key opinion leaders in child psychiatry, who have benefited greatly from industry support and appear not to have disclosed all conflicts of interest, have been active in delivering the message for the companies and in developing programmes designed to capture and increase the paediatric and adolescent antidepression markets. (p. 200)

The eagerness of pharmaceutical companies to foster commercially productive relationships with KOLs was apparent from research of over 400 internal industry documents (Spielmans &

Parry 2010). Appendix D7 contains a series of extra documents about the use of market research to typecast doctors based on their personality and prescribing habits. Once identified, 'high flyer' profile doctors who were most likely to prescribe new medications and medications off-label were targeted to establish the profit-for-outlay benefit. These doctors would then influence their peers, particularly those doctors profiled as 'rule bounds' who tend to stay "loyal to brand" (ZY100174816; Appendix D7).

It is from these ranks of 'high flyers' that KOLs may have been selected as partners by industry. A tutorial slide in a company (Eli-Lilly n.d.; Figure 9.4) gives an indication of this.

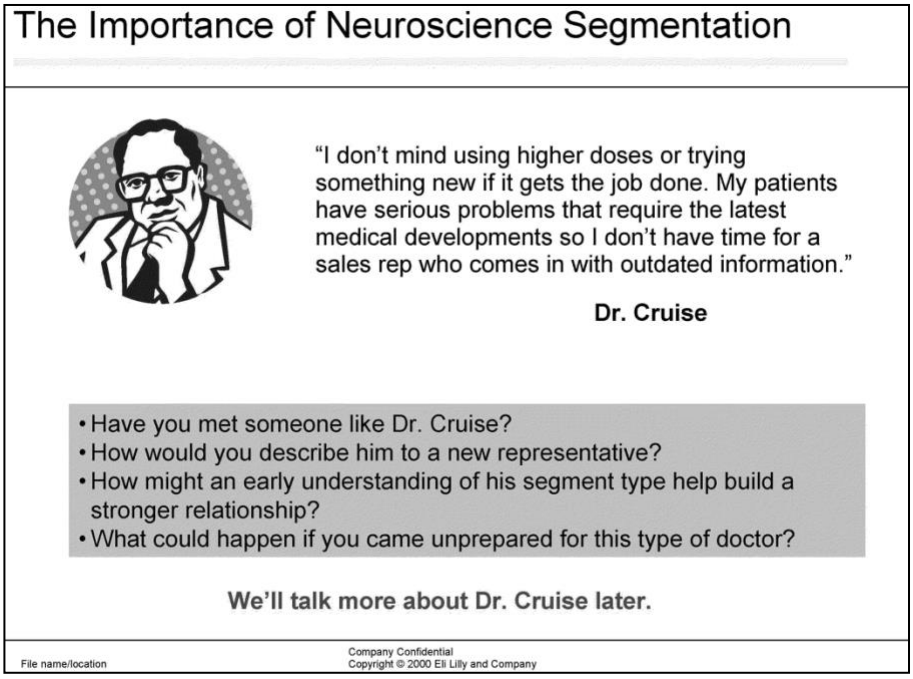


Figure 9.4: Cross-Brand Segmentation: An Introduction to Selling through Advanced Customer Knowledge ZY200085387 (Eli-Lilly n.d., p. 8)

The desire to maintain good working relationships with leading KOLs is reflected in the documents from Janssen, the subsidiary of Johnson & Johnson, (Chapter 4.2.7). It is true however, that medicine and other fields need their 'high flyers', those with entrepreneurial spirit, to push the boundaries of knowledge and innovation. The problem arises when the ethically-derived normal checks and balances of peer review, scientific scepticism and the precautionary principle, summed up in *primum non nocere,* are brushed aside by the vast sums and resources of highly profitable transnational corporations, who have their own somewhat justifiable obligation to the stock market to make money.

9.4.5.2 **Marketing bipolar disorder to the US public**

Must have bipolar indication to explode. Create a market…

Jottings on: Primary Care Physician opportunity
Zyprexa document ZY100041262
(Figure 9.5*)*

The US and New Zealand are the only high-income nations to allow DTCA. In the US, psychotropics, in particular those badged as 'mood stabilizers', have been marketed to the public as panaceas along with a meme of under-diagnosed bipolar disorder (Healy 2006). For example, TV commercials for Abilify (aripiprazole) depicted happy attractive fit people, not dissimilar to an iconic soft drink style advertisement, and helped lift sales into the blockbuster category in the US (Consumer Reports News 2009).

Healy and LeNoury (2007) described the strategic steps taken by pharmaceutical companies to enlarge a bipolar disorder market, initially with adult bipolar and then with PBD. Firstly, in the early 1990s the industry collaborated with KOL academic psychiatrists who were open to the opinion that there was an 'unmet need' of un-diagnosed bipolar disorder in the population, that the prevalence was 5% rather than 1% or less. The very term 'mood stabilizer' was created in concert with the marketing of Depakote (an isomer of sodium valproate) patented by Abbott Laboratories. The meme of unrecognised disorder was spread through academic meetings and publications and also brought to the attention of consumer self-help groups. Secondly, celebrities and lists of famous people as sufferers of bipolar disorder were circulated and appeared in magazines. Third, people were encouraged to keep mood diaries of ups and downs, which unless linked to environmental context, tended to further reify the idea that mood swings were abnormal. Astra-Zeneca created a website "IsItReallyDepression.com" with a symptoms questionnaire with a low bar for being advised to seek a mental health review for possible bipolar disorder. Fourth, risks of psychosocial failures such as divorce, alcoholism, job loss were marketed as sequelae of untreated bipolar disorder.

By this stage the US public could be considered to have been well primed and a fifth strategy of advertising via DTCA was applied. The initial commercial was produced by Lilly, the manufacturer of Zyprexa, and showed a vibrant young woman who over shops and dances

into the night but later is glum and depressed when consulting her doctor. The voiceover says: "That is why so many people being treated for bipolar disorder are being treated for depression and aren't getting better – because depression is only half the story." Viewers were then encouraged to go online to a "Bipolar Awareness Center" that also provided a questionnaire that encouraged individuals to take the results to their doctors (p. 213).

The sixth strategy, according to Healy and LeNoury (2007) involved extensive promotion at satellite symposia at the APA's 2003 annual meeting in San Francisco, where bipolar disorder was the topic at 35% of these symposia and one of the symposia was for the first time fully devoted to JBD.

As described in Chapter 4.2.2, *The Bipolar Child* book (Papolos & Papolos 2002) was a runaway best-seller that rode the coat-tails of this strategic marketing program. The publication of parent self-help and child bedtime reading books followed (Chapter 4.3.4), and the pharmaceutically-funded and KOL-supported CABF worked to further what was seen as a public health cause.

This sequence of happenings could be seen as either purely coincidental, a powerful public health awareness campaign, or a well-executed example of 'disease-mongering' (Moynihan, Heath & Henry 2002). Professor Joanna Moncrieff (University College London), noted the historical trend from anxiety neurosis when benzodiazepines were on-patent, to major depressive disorder when SSRIs were on-patent, and then to bipolar disorder where antipsychotics (rebadged as 'mood stabilizers') were on-patent (Moncrieff 2014). She summarised the concept of the "new bipolar disorder" as a "commercial success" that:

> allowed the migration of drugs such as the atypical antipsychotics out of the arena of severe mental disorder into the much larger market of people with everyday ups and downs… Academic psychiatry was complicit in this trend, which has culminated in the increasing use of these dangerous drugs in young children with behaviour problems. (p. 593)

Hand-written notes such as "must have bipolar indication to explode", "create a market", in an excerpt from an Eli-Lilly document (Eli-Lilly and Company 1999; Figure 9.5; red underline highlights added) reveal that expanding the bipolar disorder 'market' for the company's

atypical antipsychotic, Zyprexa, was a priority. It also required a “greater paradigm shift” to get primary care physicians to diagnose substantially high numbers of bipolar disorder cases, in comparison with the previous marketing of antidepressants for a more common condition. Subsequent events have shown that this strategy to increase diagnoses of bipolar disorder to ‘create a market’ for on-patent atypical antipsychotics in the US has worked (Yutzy et al. 2012).

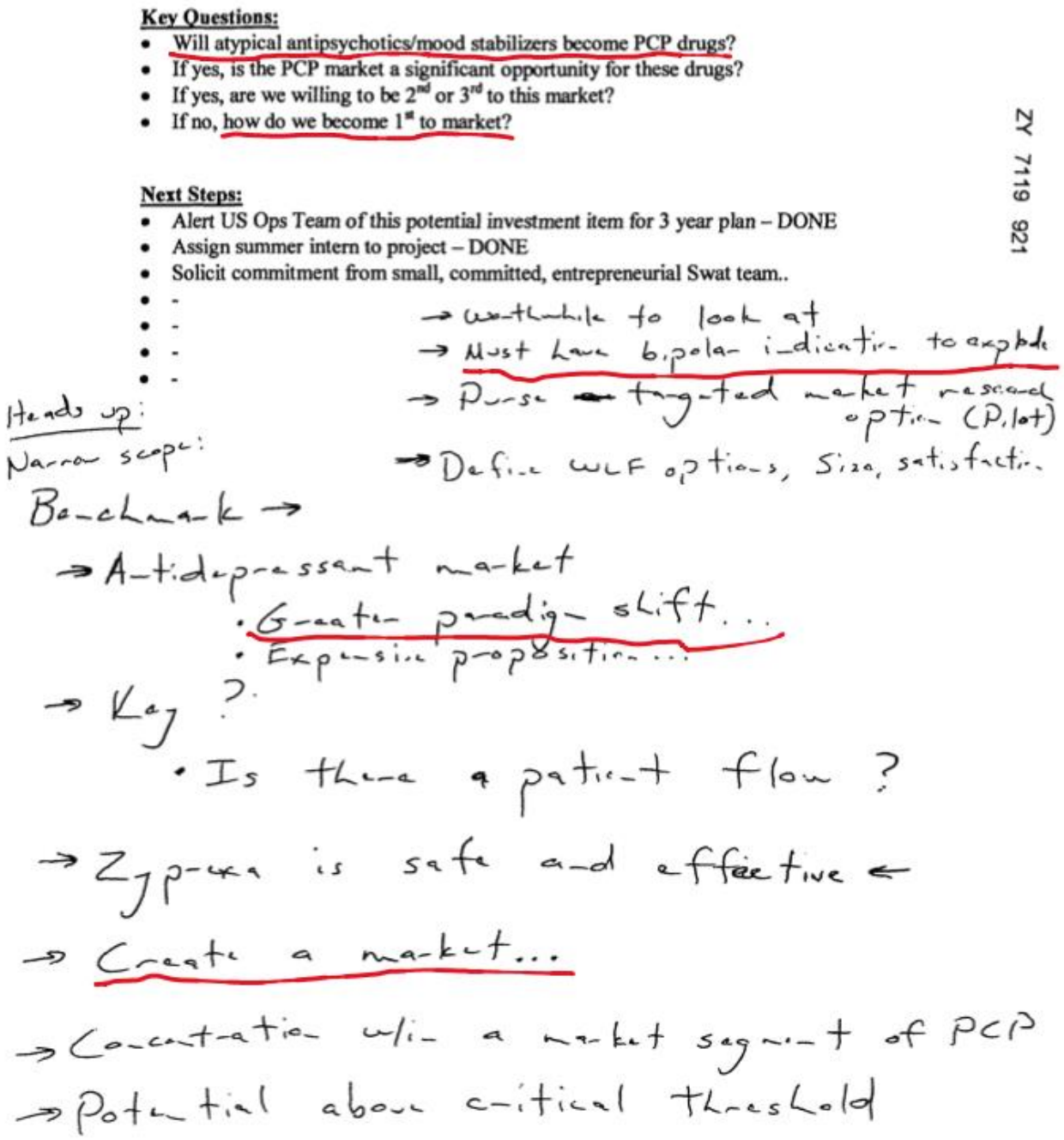


Figure 9.5: PCP Opportunity/Decision, May 7, 1999, ZY7100041262-ZY100041263 (Eli-Lilly and Company 1999, pp. 1-2)

However, although the global campaign to widen the boundaries of adult bipolar disorder spread internationally with some success, at least the same cannot be said for PBD. A PhD thesis on the topic of "Paediatric bipolar disorder in the United States and England: Psychosocial processes shaping the emergence of a contested diagnosis" (Roberts 2016),

found that the role of the pharmaceutical industry was more influential in the US than in England with both clinicians and parents:

> Results show that the pharmaceutical industry uses unstable representations of PBD, and childhood itself, to expand market possibilities of what mental illness in a child could look like. (p. 3)

After studying internal pharmaceutical documents and interviewing child psychiatrists and mental health nurses as well as parents in both countries, Roberts concluded:

> [D]iagnostic practices are driven by processes of social representation and social influence: definitions of PBD, and its emergence as a diagnosis, are extrinsic to the condition itself, forged instead at the meeting point in which actors, cultures and multiple systems of knowledge and experience interact. (p. 3)

With regards to the clinicians, Roberts found that US clinicians were influenced by "top-down" pressures from the pharmaceutical industry (p. 228) and the "education of clinicians by the pharmaceutical industry [was] a key aspect in building a particular understanding of PBD" (p. 128). The pharmaceutical industry's similar advertising to the US public led to a "bottom-up" pressure on clinicians by parents who presented as having expertise in their children's symptomatology: both perspectives were cultivated by pharmaceutical companies as embedding PBD as a variant of ADHD but requiring on-patent atypical antipsychotics. US clinicians appeared to see themselves "as a mid-point between the wider health-care system and the parent", and all were subjected to pharmaceutical company influence (p. 230).

Roberts' interviews with US child psychiatrists echo the statement of the 2019 president-elect of AACAP, Professor Gabrielle Carlson. At the height of the US PBD epidemic, Carlson described the 'top-down' and 'bottom-up' pressures upon clinicians to *The New York Times* (Chapter 4.6.10): clinicians, she said, were "inundated with stuff from drug companies ... that we're missing bipolar" (Carey 2007a) and confronted with "parents [who] very often want a quick fix" (Carey 2007b).

Conversely in England, Roberts found that academic child psychiatry took a lead in disputing the role of atypical antipsychotics for behaviour problems in very young children, citing James (2010) (Roberts, 2016 p. 104). English clinicians interviewed adhered to the classical

perspective that bipolar disorder was linked to psychotic illness and extremely rare prior to mid-adolescence. They acknowledged the US system with regard to its innovation and research but this was "tempered by a lack of trust ... due to an assumption of American clinicians practising in a culture of vested interests", indentifed as principally interests of the pharmaceutical industry (p. 232). This was despite the context of international information via the internet: Roberts found that some English parents were aware of the PBD diagnosis via online information and found the scepticism of English Child and Adolescent Mental Health Service clinicians "irritating" as they are "met with professionals who won't consider the possibility of a child having bipolar" (p. 203). This demonstrated that while clinical opinion differed in the UK, marketing strategies for bipolar disorder and PBD were playing out beyond the US.

9.4.6 **Projective identification and 'Munchausen's by Proxy'**

Parental influences on the making of a diagnosis may also have occurred for other reasons. It is traditional wisdom in child psychiatry that parents often project unresolved issues onto their offspring. The children may identify with these projections and act out accordingly. The more extreme versions of this can lead to 'Munchausen's syndrome by proxy', where a parent, through having an ill child, vicariously gains desired attention from respected medical experts for unmet and unrecognised dependency needs. For example, it appears that once 'Adam' left the home his mother resorted to factitiously produced spurious medical symptoms and diagnoses for herself.

'Adam's' father was not so available to him. Mother-son conflict is not an uncommon scenario in sole parent families with absent fathers, particularly where there has been a history of domestic violence. It often manifests when boys traverse puberty. Where there is an anxious ambivalent attachment mother-son relationship established early in development, as boys begin to physically resemble their fathers, they and their acting out rebellious behaviour, can become triggers for their mothers' unresolved trauma (Amos, Segal & Cantor 2015). As noted above, medicalisation of this dynamic provides mothers in such a predicament with a biomedical explanation that may make the mother "feel freed from the mother-blaming context … she is no longer a failed mother, but a mother battling against the odds with a disabled child" (Timimi & Maitra 2009, p. 148). This may contribute to the reality that US

prescriptions of atypical antipsychotics for boys were roughly treble that for girls (Olfson, King & Shoenbaum 2015).

Further, Healy and LeNoury (2007) noted that not only could parents have a psychological investment in the PBD diagnosis, but so too a range of others including the pharmaceutical industry, academic child psychiatry, schools and consumer advocacy groups. The authors speculated whether PBD may be a "variant on Munchausen's syndrome" (p. 219) for many of these actors involved.

9.5 Why was PBD limited mainly to the United States?

The previous chapter outlined the factors contributing to the PBD epidemic. It can be seen that the majority of these factors were located in the US. Interestingly, while other countries mostly did not experience an epidemic of PBD diagnoses, many countries did experience the ADHD and ASD diagnosis epidemics that Frances (2010b) mentioned. Various forces of globalisation and modernity, including the influence of the pharmaceutical industry, apply to nearly the whole planet. The nuclearisation and fragmentation of families, industrialised urbanised living, exposure to media (a large proportion originating in Hollywood), including the rise of social media are now facts of life across the world. These factors contributed to the proliferation of the ADHD diagnosis across borders (Timimi & Maitra 2009). Diagnostic rates of ADHD, like ASD, appear to have entered false positive territory in several countries. Further, as Scull (2010) points out, the discourse about children's behaviour problems now involves an "unscientific biobabble" that is "priceless" "marketing copy" for the pharmaceutical industry (p. 1247).

This raises the question as to why did countries that followed the US lead on ADHD and ASD not follow the US lead on PBD as well?

One probable factor appears to be the lack of similar diagnostic upcoding practices. Additionally likely to be of significance is that the biopsychosocial contextual model and a more relationship-sensitive psychiatric paradigm called for by Bracken et al. (2012) have been retained in much of international child psychiatry outside the US. A co-presentation with Professor Gordon Harper (Harvard University) (Harper 2010; Parry 2010b), included the

comment that, compared with European, Canadian or Australasian child psychiatry, this paradigm shift has not yet manifested as consistently within child psychiatry in the US.

A further marker of the spread of PBD can be found in examining the content balance of child psychiatric conference programs. For example, the number of oral presentations at each of three annual meetings on the topic of PBD in 2009 (I attended AACAP and FCAP of RANZCP; personal communication with A. Kriegeskotten, 2009, L Rusch, 2009, who both attended ESCAP) was:

- AACAP – over 40. There were a further half dozen on SMD and others on traditional interpretations of adolescent mania/bipolar disorder (AACAP 2009).
- FCAP of RANZCP – nil.
- ESCAP annual meeting in Budapest – nil.

Academic culture therefore appears to be a factor as to why PBD remained mostly, though not entirely, bound to the US. This suggests the pharmaceutical industry fostering of KOLs for PBD was mostly confined to a few US academic departments. It must also be remembered that many large US child psychiatry departments are conspicuously absent from the PBD literature, so although PBD had prominent US academic support, there were US academic centres that did not support the PBD hypothesis (Chapter 7). The cooperation of KOLs with the CABF and its lobbying and advertising through the US media played a role within the US, but the same did not occur for PBD in other countries.

CONCLUSION

In coming to this thesis and seeking to understand the presenting phenomenon of the PBD epidemic, I have utilised as an external framework the diagnostic formulation template for organising possible contributory factors (Chapter 9.4.1.2). These have been arranged as to whether they could have predisposed, precipitated and/or perpetuated the PBD epidemic, as well as any protective factors that may have limited its spread. What follows is my 'dynamic diagnostic formulation' as to why the PBD phenomenon unfolded as it did, a prognosis about possible future fates for the PBD hypothesis, and a 'management plan' as to how to address some of the underlying factors.

Dynamic diagnostic formulation of the PBD phenomenon

The presenting phenomenon of PBD originated as a research hypothesis developed by two prominent US child psychiatry departments of WUSL and MGH-Harvard. It was enthusiastically adopted by a modest number of other US academic departments. What followed was a premature translation into relatively widespread clinical practice within the US, although some US academic departments did not publish on the diagnostic hypothesis, and there were child psychiatrists critical of PBD within the US.

While the concept failed to deeply penetrate many non-US jurisdictions, it was embraced by several child psychiatry academic departments in Mediterranean and Latin American nations who collaborated with US PBD researchers (e.g. Spain, Italy, Turkey, Brazil) and recently in South Korea.

The **predisposing** factors to this epidemic include: (1) a very real and genuine desire for early intervention and detection of major mental disorder, in this case the historically rare but serious condition of bipolar disorder; (2) a global paradigm shift in psychiatry, perhaps most apparent in the US, towards a biomedical reductionist 'mindless psychiatry' perspective; and (3) the increasing influence of the pharmaceutical industry in the field of psychiatry. While the goal to identify and treat disorders early continued, the other two factors had a corrosive effect on US psychiatric training as psychoanalytic, psychodynamic, family systems perspectives and indeed the biopsychosocial model itself faded from prominence (Tasman 1999).

A related predisposing factor was the minimal consideration of the impact of child abuse and attachment trauma. This may likely relate to the individual and societal tendency to defend against overwhelming trauma that has manifested in individual and group repression or non-disclosure of childhood maltreatment. Psychiatric nosology, has not been immune to this dynamic and has a history of tending to minimise the role of trauma, as exhibited by the very recent modification of the PTSD criteria for young children exposed to domestic violence for the 2013 fifth edition of the DSM. This was reflected in the minimalistic consideration of such trauma and maltreatment factors, and even bedrock developmental concepts as attachment theory in the PBD literature (both in terms of theory and assessment practices in research). In turn, this allowed for a reification of symptoms that otherwise would have indicated distress and survival defences of fight/flight/freeze/appease, dissociation and magical thinking, to be misinterpreted as irritability, increased activity, grandiosity, delusional thinking and euphoria. Thus, normative stress reactions, or reactions mediated by pathological levels of anxiety and hyperactivity-distractibility, were instead attributed to mania and mixed affective episodes even though they deviated from DSM and ICD criteria by being chronic and/or cycled several times per day.

Precipitating factors for the epidemic included the pharmaceutical industry's need for a multiplication of cases of previously rare bipolar disorder diagnoses to "create a market" (Figure 9.5) for new and on-patent atypical antipsychotic drugs as the SSRI generation of drugs began to go off-patent. This led some pharmaceutical companies to seek out and "foster" the "careers" (Scull 2010, p. 1247) of academic KOLs who believed in the PBD hypotheses, as well as financing widespread CME to clinicians about the new disorder. The principal precipitant to US public awareness of PBD as a putative answer to serious child and adolescent emotional and behavioural problems was the pharmaceutical industry's DTCA advertising and sponsorship of patient self-help groups such as the CABF/Balanced Mind Foundation, plus a genre of PBD books for parents and children.

Major **perpetuating** factors likely included: (1) a lack of universal health cover within the US that rationed health care to many with limited or no insurance cover meaning they were more likely to receive pharmacotherapy and less likely to have avenues to non-drug therapies; (2) managed care health systems dominating clinician freedoms such that many psychiatrists and paediatricians were forced into brief 'med check' appointments and pressured into

'diagnostic upcoding' practices to obtain insurance reimbursements for themselves and their patients; (3) deskilling of psychiatrists and lack of skilling for behavioural paediatricians in play-therapy, parent-training, parent-child dyadic therapy, CBT and other individual and family psychotherapies, leaving them overly dependent on prescribing pharmacotherapy; (4) for some parents, families, schools and other agencies, the idea of a simple answer to complex problems in the form of a hoped for simple 'pill fix' provided reassurance and comfort and a way to avoid solutions that may have been more painful or difficult; (5) for KOLs and other PBD researchers, in the 'publish or perish' atmosphere of academia, an ongoing pressure to continue to research and validate the PBD hypothesis; (6) such PBD literature providing a sense of validity to diagnosing and pharmacotherapy practices of physicians who for the preceding suggested reasons had become overly dependent on prescribing.

Protective factors preventing and limiting the spread of the PBD epidemic within the US appear to have been academic centres and clinicians who have continued to adhere to the traditional biopsychosocial developmental perspectives on psychopathology and classical framework of bipolar disorder. Additionally, the work of Liebenluft at the NIMH and colleagues to coin the new diagnostic category of DMDD into DSM-5 specifically to curtail the US PBD epidemic provided an authoritative cautionary message to clinicians and researchers.

Potential protective factors in other countries included: child psychiatry research centres being publicly funded and receiving less pharmaceutical industry sponsorship; adherence to traditional child psychiatric training models; and importantly, universal single-payer government subsidised health care systems. Such health systems, in contrast to US privatised managed care, tend to put less emphasis on allocation of resources by diagnosis and discriminate less against non-drug interventions. Restrictions on DTCA marketing and an absence of KOL or senior academic support in self-help organisations, or books and media promulgation of the PBD hypothesis also appear to have been protective. However, such protective factors can be negated whenever sufficient circumstances induce diagnostic upcoding. For example, the monetary and educational resources tied to an ASD diagnosis in Australia has arguably led to an overdiagnosis epidemic of ASD (Chapter 5.1.1).

Prognostically, it is unclear how long the PBD epidemic will persist and if it will spread further internationally in places like southern Europe, Latin America and East Asia. With the

publications of articles on SMD from 2006 (Brotman et al. 2006) and passage of DMDD into the lexicon of the DSM, and the conflict of interest controversy in the wake of the Senator Grassley inquiry, the peak of publications on PBD appears to have possibly been reached in 2009 (Figure 4.1; Figure 4.38). Despite some ongoing publications, the 'broad phenotype' MGH-Harvard hypothesis has faded. The 'narrow phenotype' WUSL hypothesis has been taken forward by the Pittsburgh group as Bipolar-NOS in the COBY study and BIOS offspring study.

However, several other US and international high-risk offspring studies now clearly support the classical perspective of late adolescent onset of bipolar disorder (Chapter 4.8.7). As demonstrated in Chapter 6, a systematic review of the epidemiological surveys used for the key meta-analyses that found high community prevalence of 'PBD' (Van Meter, Moreira & Youngstrom 2011; 2019b), found pre-adolescent cases of bipolar disorder to be very rare and adolescent cases rare when informant concordance was sought. More recently, follow-up studies into adulthood have found adolescent hypomania a poor predictor of adult bipolar disorder (Päären et al. 2014; Tijssen et al. 2010a; Chapter 6.8.3.4). Additionally, national discharge diagnosis studies from Europe and Australasia, published since 2014 have also agreed with the classical perspective of only extremely rare cases of hypomania/mania before mid-adolescence (Chapter 4.8.6.14). These studies will continue to provide researchers and clinicians around the world with further reasons to question the PBD hypothesis and avoid making a false bipolar disorder diagnosis.

The iatrogenic consequences of erroneous diagnostic and management practices has been seen previously in psychiatry with one of the worst cases being the practice of frontal lobotomies affecting thousands. Now juvenile animal studies raise the possibility that a mild form of iatrogenic pharmaceutical induced 'frontal lobotomy' may be being visited on millions of children through the medium of atypical antipsychotic prescriptions. The PBD epidemic played a pivotal role in this widening of use of atypical antipsychotics for young children. Whether future psychiatrists will consider "the diagnosis of pediatric bipolar disorder [as] the greatest scandal to ever befall psychiatry" (Paris 2012; Prologue, p. 21), time will tell.

Management plan

For decades it has been axiomatic in child psychiatric training and practice that a well-constructed biopsychosocial formulation of a child and family's mental, emotional and behavioural problems leads to an accurate diagnosis with all the attendant contributory factors understood in their context. This diagnostic formulation then forms the basis for a therapeutic management plan.

In a similar manner, exploring and understanding the contributory factors to the PBD epidemic leads to potential solutions to address both the epidemic and its consequences, that could improve the practice of child and adolescent psychiatry internationally.

The suggestions for quelling the PBD epidemic and providing a best practice approach to assisting emotionally and behaviourally dysregulated children and their suffering parents and families include (with suggested responsible agencies for change):

- Preserve and expand the biopsychosocial model in paediatric, psychiatric and allied mental health training and clinical practice. In light of 'diagnostic epidemics', expand consideration of how wider factors such as industry marketing can affect whole nations and cultures, therefore a sophisticated biopsychosociocultural model is the most useful. Furthermore, given the complexity of humanity, the 'four perspectives' model (Chapter 9.4.1.3) would appear a necessary dimensional addition to the biopsychosocial model (training committees of psychiatric and paediatric colleges/universities/associations).

- Emphasise the particularly potent role that attachment disruption, developmental trauma and child maltreatment factors play, interacting with children's inborn temperament and genetic vulnerabilities. Child protection services and practical family respite and support services are often under-resourced and need to be upgraded and more fully utilised globally (child and infant general and mental health associations; governmental social services).

- Utilise the large body of developmental trauma literature, which includes neuroimaging research findings of the effects of maltreatment and attachment

disorganization on children's developing brains (organisations funding research; academic research units).

- Undertake a necessary deep revision of psychiatric nosology, as called for by numerous individuals and groups such as the British Psychological Society and the American Psychological Association's Division 32 in their open letter to the APA (CDR 2011). As an editorial in the *American Journal of Psychiatry* (Denton 2007) commented, the lack of the "consideration of the role of relational processes" in the mental disorders classified within the DSM has been a "deficiency" (p. 1146). DSM-5 did introduce a subtype of PTSD for children aged 6-years-old and younger that included consideration of domestic violence, yet overall it did not rectify this limited consideration of relational context. The difficult task to fully incorporate the psychosocial, cultural, developmental and, as Spitzer (Horowitz & Wakefield 2007) later admitted, contextual factors into a still usable psychiatric nosology manual lies ahead. One useful starting point would be to review the research for the proposed DSM diagnosis of Developmental Trauma Disorder (van der Kolk 2005). Inclusion of Developmental Trauma Disorder in the DSM would draw attention to the above vital contextual factors (the committees and working parties of the DSM and ICD).

- Implementation and research of the Power-Threat-Meaning Framework proposed by the British Psychological Society (Johnstone & Boyle, 2018; Chapter 9.4.5.1) would further the diagnostic and therapeutic focus onto psychosocial aetiological factors and shift focus away from an overly biomedical reductionist approach.

- Study the under-researched phenomenon and clinical application of 'undiagnosing' (Patfield 2011) patients of erroneous diagnoses, and the myriad effects of 'labelling' in their lives (organisations funding research; psychiatric and paediatric research committees).

- Study the neurological effects of atypical antipsychotics, particularly on the developing brains of children and adolescents, in the light of evidence suggesting neutoxic cerebral atrophy (organisations funding research; psychiatric and paediatric research committees).

- Health and education systems need to cease fostering 'diagnostic upcoding' with arcane bureaucratic rigidity, that skew understanding and treatment. Adequate time and remuneration for clinicians to gain rapport, understanding and a full diagnostic formulation followed by implementation of therapies as indicated – including child play-based therapies, addressing developmental delays such as speech therapy, parent-child dyadic therapy, parent-training courses, family therapy, adolescent psychotherapy, CBT, mindfulness and Dialectic-Behaviour Therapy (DBT) and group therapies, and where appropriate – adjunctive pharmacotherapy (child psychiatry and paediatric college leadership and collaboration with health insurers and education authorities).

- The emerging consensus from the high-risk offspring studies, does indicate that the early stages of true bipolar disorder may be suspected before manifestation of the first clear-cut hypomanic or manic episode. However, the early syndromes of sleep and anxiety disorders and vulnerability to minor and major depressive episodes in childhood and early adolescence remain non-specific. In the case of strong family history of Bipolar-I or Schizoaffective disorder, then watchful waiting, reducing stressors and improving resiliency plus pharmacotherapy if future research supports its use would be the best approach (the ISBD Prospective Offspring Studies and Treatment Trials Task Force consulting with and communicating results to psychiatric and paediatric college/association training committees) .

- Intervene to address conflict of interest relationships between the pharmaceutical industry and the medical profession (collaborative approach between government and medical colleges/associations).

  A further protective factor against conflict of interest is data transparency, as advocated by the *'AllTrials'* campaign (www.alltrials.net). As well, the Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, (2009) listed 16 detailed recommendations for positive change, with the more salient ones being:

  - Full public disclosure of all finance between industry and physicians, researchers, public advocacy groups, providers of CME etc. (recommendation 3.4)

- Academic centres to not permit researchers to conduct research where they have a significant financial conflict of interest (4.1)
- "[P]rohibit … gifts … [and] controlled presentations by industry" and ghost-written papers (5.1)
- Goal for CME to be "free of industry influence" (5.3)
- Clinical practice guidelines committees' members to be free of conflict of interests, "in the exceptional situation" where this is "impossible", then as well as extensive disclosures, "appoint a chair without a conflict of interest" (7.1)

- (These responses to conflict of interest require coordination across speciality college committees, government regulators, the pharmaceutical industry and could possibly be best be informed by the academic leadership that has congregated through the *AllTrials* campaign).

Limitations of this thesis

The general limitation of this thesis follows from the presence of different paradigms operating within international child and adolescent psychiatry and psychiatry more broadly. As presented in the Prologue, the viewpoint brought to this exploration of the PBD diagnosis epidemic phenomenon has been that of a clinician trained within the FCAP of the RANZCP who has practised in Australia and the UK. It is not so much a limitation, but a perspective that needs to be considered by the reader. It applies in Part I and Part II as to how the literature and events associated with the PBD phenomenon have been understood and discussed.

It also applies to the perspective brought to the novel research in Part II, however in Part II there are some more specific limitations as well:

Firstly, in Chapter 6 the narrative re-analysis of the epidemiological surveys used for statistical meta-analysis (Van Meter, Moreira & Youngstrom 2011, 2019b) did not explore the statistical mathematics used by Van Meter et al. Rather, the original published versions of these epidemiological surveys were closely read and it was deduced from the methodologies described that rates of bipolar-I and bipolar-spectrum disorders were generally significantly lower than the summative rate given by the meta-analyses. Some questions regarding

methodological details were answered in emails by the original epidemiological researchers. The perspective taken in deriving our results was also naturally affected by the dominant paradigm of bipolar disorder in RANZCP training and Australian clinical practice.

Secondly, the limitations inherent in examining the academic perspectives towards PBD from a geographical perspective are outlined in Chapter 7.4.5: the full PBD literature was not sourced, but a 'citation tree' portion of it derived from four key early PBD articles and these four articles were of US origin only; and there was a risk of bias in selecting the 'perspective' of the articles as this was a task undertaken solely by myself as the principal investigator. To deal with this latter limitation, examples are presented (Chapter 7.2.4) and the full lists of the citating articles with assigned 'perspective' available (Parry, Allison & Bastiampillai 2019b, online supplementary material; Appendices C1-3).

Thirdly, the limitations of the bibliometric review of the PBD literature for attachment and developmental trauma terms are outlined in Chapter 8.5: the body of PBD literature that was accumulated and the search terms 'attachment', 'trauma', 'PTSD', 'abuse' and 'neglect' depended on the *Scopus* academic database and search function. The terms were searched in "title, abstract, keywords, references" of all 1,113 PBD-related articles up to date 15 June 2010, but not in the full texts of such articles in the *Scopus* search. However, these attachment and developmental trauma terms were examined for use in the full texts of: (1) all 15 articles that mentioned 'attachment' in either their title, abstract, keywords or references; (2) all 64 articles affiliated with authors from WUSL; and (3) all 137 articles affiliated with authors from MGH-Harvard (Chapter 8.2.2).

Fourthly, this thesis could be critiqued for not beginning with a systematic review of the whole PBD literature. However, Part I examined in chronological fashion most of the more prominent PBD-related publications starting with the classical literature regarding early-onset bipolar disorder, incorporated major PBD review articles and highlighted notable debate. Part II included two large bibliometric literature reviews of 787 and 1,113 articles, and space considerations moved an in-depth analysis of the 787 citation-tree articles to Appendix C6. The size of the PBD literature and the classical bipolar disorder literature is discussed in Chapter 4.8.9.3. The specific PBD literature, according to a more specific *Scopus* search (Figure 4.38) amounts to less than one thousand articles. Thus, it is unlikely that significant numbers

of PBD articles with substantive new information, that would have affected the conclusions drawn here, have been missed.

Summary

This thesis provided a chronological exploration of the origins and spread of the PBD hypothesis that mania presented atypically in childhood and early adolescence. Three research questions that explored the PBD phenomenon were addressed with: (1) a narrative re-analysis of epidemiological studies that found claims of high community prevalence of PBD could not be supported; (2) a bibliometric review of PBD publications examining the geographic affiliations of authors according to whether they were proponents of PBD or adhered to the classical perspective of late adolescent-onset of mania, that found spread of the PBD hypothesis remained mostly confined to several US and a small number of non-US academic institutions; and (3) a bibliometric literature review examining the presence or absence of consideration of attachment and developmental trauma in the PBD literature, that found such consideration was mostly absent.

The PBD phenomenon has been referred to as an 'epidemic' (Frances 2010b) and a 'scandal' (Paris 2012). This thesis has sought to explore how a research hypothesis was rapidly translated into clinical practice, and identify the likely predisposing, precipitating and perpetuating contributory factors that interacted to produce an epidemic that was mostly confined to the US. In doing so, evidence has been presented of the iatrogenic consequences of the PBD epidemic, which included substantial adverse drug effects. Evidence of diagnostic upcoding factors, more particular to the US health system than most other countries, have been explored. Examination of pharmaceutical industry documents suggest lapses in strict attention to principles of medical and scientific ethics had occurred. Further, a critical factor appears to have been problems inherent in psychiatric nosology as encapsulated in the 'descriptive' symptom-focused and decontextualized application of DSM criteria that fails to explore insecure attachment, maltreatment and family stressors as factors provoking emotional and behavioural symptoms in children and youth.

Nevertheless, the timely early diagnosis of true hypomania/mania and thus bipolar disorder remains of vital importance and the search for antecedent syndromes continues, particularly

through longitudinal high-risk offspring studies. There are signs that the number of publications in the PBD literature is decreasing, but many children and adolescents are still being labelled with the diagnosis. This exploration of the PBD phenomenon suggests it is a hypothesis that should never have been reified and clinically applied. In order to best understand and intervene in child and adolescent emotional and behavioural dysregulation, as well as accurately diagnosis bipolar disorder when it does occur, it is imperative that the mental health field learn the many lessons of the PBD epidemic.

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