Appendix A:

Publications relevant to this thesis

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NB: Appendices A6 & A11 (landscape format conference posters) are in a separate file.

Correspondence

Simpler explanation for catatonia

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Pridmore and Rybak described four patients with catatonic syndromes who were able to use a mobile telephone when they apparently could not speak to other relatives or staff in person [1]. This peculiarity '... can raise questions about the patient being selective or manipulative, and call the diagnosis into question'. However, they felt that there was no doubt as to the validity of the diagnoses, and I am sure they were correct. Although increasingly rare, the features of the catatonic state are indubitable.

In my view their observation does not raise doubts about the diagnosis but about the nested assumptions upon which the diagnosis depends. These are, of course, the assumptions of reductionist biological psychiatry; essentially, that the clinical features are reducible to a physical lesion at the neuronal or subneuronal level in the brain. This belief drives the biological program in psychiatry [2] but is without warrant [3]. Reconceptualizing catatonia in simpler, different terms does justice to the observed features without setting up impossible constraints. If the condition is seen as a self-perpetuating state of psychologically determined hyperarousal, then there is no problem with the notion that, if they feel safe, the patients can briefly override the clinical syndrome. In more technical terms, a programming error can always mimic a physical fault in a Turing universal computing machine, but not vice versa.

The authors hinted at this but did not seem to see its full significance: 'The telephone ... may allow communication ... without the arousing effect of (people's) physical presence'. That says it all: catatonia is a psychologically determined condition, which helps explain why it is going out of fashion.

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Ethnic differences in prevalence of bipolar disorder in Te Rau Hinengaro: the New Zealand Mental Health Survey

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An interesting insight into the presentation of bipolar disorder in a non-representative sample of service users in New Zealand is provided by Mellsop *et al*. [1] using data from the CAOS study [2]. These authors show that for both manic and depressive presentations in bipolar patients, Health of the Nation Outcome Scale (HoNOS) ratings of overactivity/disruptive behaviour were higher for Māori than for Europeans. They argue that overactivity and disruptive behaviour may have been mistaken for symptoms of bipolar disorder in Te Rau Hinengaro, the New Zealand Mental health Survey (NZMHS) [3], resulting incorrectly in higher reported prevalence of bipolar disorder for Māori. We disagree.

We note first that unfortunately Mellsop *et al*. did not take into account age or sex, let alone socioeconomic status, so that it is unclear to what extent these may have confounded their ethnic comparisons. Because a number of forensic services were included, it seems likely that there were more young men among their Māori bipolar patients so the European/Māori difference may reflect age and sex differences, not ethnicity per se.

Mellsop *et al*. state that in the NZMHS lay interviewers were deciding on the presence or absence of phenomena without the contextual knowledge clinicians use. This shows a misunderstanding of the nature of fully structured interviews such as the Composite International Diagnostic Interview (CIDI) [4]. In order to allow the use of trained lay interviewers all questions are completely pre-specified. Interviewers do not rate, they record responses. If one group are diagnosed with a higher prevalence than another group this is because they have been more likely to report enough symptoms to meet criteria [5].

Mellsop *et al*. also contend that the clinician-derived diagnosis of bipolar disorder in the CAOS

Appendix A1

must be more accurate than a CIDI 3.0 diagnosis. They do not describe the procedure by which the diagnoses were derived by the clinicians in the CAOS, nor do they provide any evidence about the reliability and validity of the procedures to support their contention. It has been known for some time that diagnoses derived from unstructured clinician interview are problematic both in terms of reliability and validity [6]. Similarly, they provide no information about the reliability or validity of the HoNOS in their study. Mellsop *et al*. base their argument on their findings of ethnic differences in mean ratings on item 1 (overactive, aggressive, disruptive or agitated behaviour) of the HoNOS. In a review of the instrument, Pirkis *et al*. noted that although interrater reliability of item 1 is good to moderate, the test–retest reliability is poor [7].

There has been a clinical validation study for bipolar disorder in the US National Comorbidity Study Replication (NCS-R) [8]. In that study clinical reappraisal did not indicate overdiagnosis with the CIDI 3.0, which was unbiased compared to the clinician-administered Structured Clinical Interview for DSM-IV (SCID) for lifetime disorder.

There are now three sources of data on the prevalence of bipolar disorder in different ethnic groups in New Zealand. One is the NZMHS, a nationally representative community survey in which the 12 month prevalence was found to be 4.6% for Māori and 1.8% for Others (non-Māori, non-Pacific), although this difference was reduced after control for age and sex to 3.8% versus 1.8%, and further reduced to 3.4% versus 1.9% after additional control for education and income [3]. The second is hospitalization data, which shows that age- and sex-standardized inpatient discharge rates were 2.4-fold higher in Māori than in non-Māori [9]. The third is the CAOS that, as Mellsop *et al*. report, included only services that volunteered to participate, so that 'Incidence and prevalence figures cannot be extrapolated from these findings and applied to the general population' [2]. In CAOS apparently there were no ethnic differences in the rates of diagnosis of bipolar disorder. Because the services were not taken from any defined population base it is not clear how any rates could be calculated from the CAOS data. Does this claim mean merely that the percentage of service users with bipolar disorder did not differ by ethnicity? This could occur if Māori had higher rates of other disorders as well, as is shown in the hospitalization data for schizophrenia [9]. Under this scenario the percentage of hospitalised cases with a particular disorder can be equal for each ethnic group even though the community prevalence differs and even when the percentage of cases admitted differs across ethnic groups.

In conclusion, the critical appraisal of Mellsop *et al*. of the NZMHS findings with respect to ethnic differences in bipolar disorder does not take into account the problem of confounding by age and gender, or the non-representative sample of the CAOS. Furthermore, the argument put by Mellsop *et al*. assumes that the lay person-administered CIDI 3.0 overestimates caseness compared to a clinician assessment, whereas the available evidence does not support this contention. There is much still to be learned about the presentation of bipolar disorder and the prevalence of symptoms across different groups in New Zealand, but we are not convinced that the Mellsop *et al*. study has provided an explanation of the ethnic differences found in the NZMHS.

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Paediatric bipolar disorder is a controversial diagnosis

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The editorial 'Growing evidence to support early intervention in early onset bipolar disorder' (BD), by Mao and Findling in the August issue of the Journal is one of the first papers on paediatric bipolar disorder (PBD) in the Australasian psychiatric literature [1]. But Mao and Findling give no indication of the extent of controversy surrounding the diagnosis of PBD, in particular pre-pubertal PBD. For example, in contrast to the *Australian and New Zealand Journal of Psychiatry* editorial, the February 2007 editorial of the *American Journal of Psychiatry* noted: 'Pediatric bipolar disorder is notoriously controversial, with the epicenter of the debate being whether the condition can be diagnosed in pre-pubertal children at all' [2].

The Australasian literature needs to be informed of this debate because although research into whether antecedents of BD exist in young children is laudable, our concern is that the *Aust N Z J Psychiatry* editorial may inspire increased use of antipsychotics and mood stabilizers among children and adolescents before either diagnosis or benefits are clear and these children will run the risk of serious side-effects.

Mao and Findling do acknowledge that 'many clinicians are still reluctant to treat children and adolescents ... with symptoms suggestive of a BD diathesis' and that it is a 'challenge to accurately diagnose ... PBD'. Nonetheless they appear to take as a given that BD, or at least 'cyclotaxia' (Findling's term) referring to subsyndromal affective symptoms, can be diagnosed in children as well as adolescents.

In the USA there is rising controversy in both the academic literature and the public media fuelled by a rapid rise in diagnosis. Recent research shows a 44-fold increase in diagnosis of BD in the under-20 age group between 1994–95 and 2002–03 [3]. Concern over use of antipsychotic and mood-stabilizer medication in very young children follows the highly publicized death of a 4-year-old girl who was diagnosed with BD at age 28 months [4]. A study of 118 paediatric psychiatric patients aged 5–18 years on atypical antipsychotics for at least 6 months found that 11 (9%) had tardive dyskinesia [5].

Also in contrast to the *Aust N Z J Psychiatry* editorial, the July 2007 issue of the *Canadian Journal of Psychiatry* carries an editorial entitled 'Controversies in childhood bipolar disorders' [6], and while one lead paper maintains that the construct is valid the other lead paper by Duffy questions the existence of pre-pubertal PBD [7]. Duffy notes that while there is evidence 'in some cases of prodromal psychiatric disturbances' in offspring of parents with well-characterized BD, that in longitudinal studies of these offspring 'there have been no observations of diagnosable BD in children under the age of 12 years'.

Duffy goes on to critique the PBD research literature in the way others have. The research is mainly predicated on phenomenology and tends to ignore developmental, traumatic and family dynamic issues. A relationship-based approach to understanding young children's behaviour is essential for diagnosis.

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.

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Growing evidence to support early intervention in early onset bipolar disorder?

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Reading the Editorial 'Growing evidence to support early intervention in early onset bipolar disorder' by Mao and Findling in the August issue of the Journal [1], reminded us of the story of the Emperor's new clothes.

The views of Mao and Findling, given editorial status without any critical comment, appear to reflect a widespread view among psychiatrists that early intervention should be embraced even in the absence of evidence of benefit and in the face of clear evidence that some early interventions can be harmful.

The authors argue that because bipolar disorder (BD) appears to be associated with progressive worsening over time, treatment should begin early in the course of illness. This would be a reasonable argument if (i) those who will develop the illness are able to be identified; (ii) the intervention was helpful at the time it was administered; and (iii) the intervention improved the long-term course of the disorder. Nothing in the Mao and Findling paper persuaded us that any of these criteria had been satisfied.

First, BD as described by Mao and Findling appears to be ill-defined. Terms such as 'cyclotaxia', 'bipolar disorder not otherwise specified' and 'youths with subsyndromal symptoms' would describe a heterogeneous group of troubled young people of whom an uncertain proportion will develop BD.

Second, the only placebo-controlled trial quoted by Mao and Findling (their own) showed no difference between the active treatment (divalproex sodium) and placebo. Surely the correct conclusion from that study is that there is no evidence for effective pharmacological therapy for those identified as being at high risk for bipolar disorder. Instead the authors state that 'regardless of whether or not these children will develop BP-I, these children deserve early and effective treatment' although they do concede that they 'may not necessarily require pharmacotherapeutic interventions'.

Third, no evidence was presented that early intervention does change the long-term outcome of the disorder.

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. Presumably they are motivated by the need for early intervention.

We are also concerned that the 'growing evidence for early intervention in bipolar disorder' seems so unconvincing and we are concerned that the Journal allows the publication of such an article as its editorial, without comment.

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CHILD AND ADOLESCENT PSYCHIATRY

Pre-pubertal paediatric bipolar disorder: a controversy from America

Peter Parry and Stephen Allison

Objective: *The aim of this paper was to explore the rapid rise in the diagnosis of bipolar disorder (BD) in the paediatric, particularly pre-pubertal, age group, in the USA over the past decade and to look at associated controversies.*

Conclusions: *There has been a very marked rise in the diagnosis of BD among pre-pubertal children, and to a lesser extent adolescents, in the USA since the mid 1990s. The rise appears to have been driven by a reconceptualizing of clusters of emotional and behavioural symptoms in the paediatric age group by some academic child psychiatry departments, most notably in St Louis, Boston and Cincinnati. There is controversy in both the academic literature and public media centring on diagnostic methods, epidemiological studies, adverse effects of medication including media-reported fatalities, and pharmaceutical company influence. With some exceptions, the traditional view of BD as being very rare prior to puberty and uncommon in adolescence appears accepted beyond the USA, though whether this is changing is as yet uncertain, and thus there are implications for Australian and New Zealand child and adolescent psychiatry.*

Key words: *pre-pubertal paediatric bipolar disorder, USA.*

THE PHENOMENAL RISE OF BIPOLAR DISORDER IN THE PAEDIATRIC AGE GROUP IN THE USA

Over the past decade, there has been a surge in the numbers of children and adolescents diagnosed with bipolar disorder (BD) in the USA. For example, the number of visits to GPs in the USA in the under 20 age group where the diagnosis was BD increased from 0.01% in 1994/1995 to 0.44% in 2002/2003.[1] BD is now the most common diagnosis in children under age 12 years receiving psychiatric hospitalizations according to data from the Centre for Disease Control.[2]

Time magazine's cover story on 11 August 2002, ''Young and Bipolar'', reported that ''... experts estimate that an additional 1 million preteens and children in the U.S. may suffer from the early stages of bipolar disorder''.

A range of parent-oriented support groups and websites have arisen. The website www.BPchildren.com asserts that BD can begin in infancy and www.bpkids.org asserts that many or most cases of attention deficit hyperactivity disorder (ADHD) are in fact BD or have comorbid BD. Several books by psychiatrists strongly advocate for recognition of widespread paediatric BD:

- *The Bipolar Child*,[3] subtitled ''The definitive and reassuring guide to childhood's most misunderstood disorder'', sold over 200 000 hardback copies and is now into its third edition;

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doi: 10.1080/10398560701829592

- *Bipolar* Kids,[4] which is reviewed on the author's website[5] with a statement: ''once considered an adult illness, bipolar disorder (manic depression) is one of the fastest growing categories in child psychiatry since ADHD, touching the lives of an estimated one million children'';
- *Bipolar not* ADHD;[6]
- *Pediatric Bipolar Disorder: A Handbook for Clinicians*,[7] which advocates medicating in the preschooler age group.

There are also self help books in the colouring-in and bedtime story genres such as *My Bipolar Roller Coaster Feelings Book*[8] and *Brandon and the Bipolar* Bear.[9] In the latter, Brandon is told by his doctor that behaviour he thinks is 'bad' is not his fault but an inherited illness, and he will get better with medication. The back cover review by Janice Papolos, co-author of *The Bipolar Child*, states:

> ''... children will follow Brandon's experience with rapid mood swings, irritability, his sense of always being uncomfortable and his sadness he can't control himself and no-one can fix him. The comforting explanation that Dr Samuel gives him makes Brandon feel not alone, not bad, but hopeful the medicine will make him feel better. We were so moved by the power of this little book ... we highly recommend it for children aged 4 through 11''.

EPIDEMIOLOGICAL EVIDENCE?

Despite the quoted high rates, there is little supporting epidemiological evidence, though this may change when newer survey instruments reflecting changing criteria are used[10,11] or older ones like the Child Behaviour Checklist (CBCL) are reinterpreted for BD.[12]

A survey of 1709 American high school students aged 14 to 18 years[13] found a lifetime prevalence of bipolar disorders (primarily bipolar II disorder and cyclothymia) was approximately 1%. Although an additional 5.7% of the sample reported distinct periods of elevated, expansive or irritable mood, they did not progress to have BD in their 20s.[14] The Great Smokey Mountains Study of 4500 9–13-year-olds in the Appalachian region of the USA[15] found no cases of mania and a 0.10% 3-month prevalence of hypomania, while other prevalence rates were anxiety disorders 5.7%, conduct disorder 3.3%, oppositional defiant disorder 2.7% and hyperactivity 1.9%.

ACADEMIC UNDERPINNINGS OF THE SURGE IN DIAGNOSIS

The rise in diagnosis of a disorder traditionally considered extremely rare in pre-pubertal children and at least uncommon in adolescence, appears related to a shift in criteria for BD when it occurs in paediatric populations and is distinguished from the phenomenology of adult BD.[16] Two centres in the USA, the group of Biederman, Wozniak and colleagues at the Massachusetts General Hospital, Boston, and the group of Geller *et al.* at Washington University, St Louis, have led the way in research, claiming much higher rates of paediatric BD. A third group of Kowatch, Delbello[17], Keck[18] and others, based in Cincinnati, Ohio, accept both constructs and have been prominent in the promulgation of treatment guidelines for paediatric BD.

The 'Broad Phenotype'

The Biederman and Wozniak group see irritability as the key feature of paediatric BD and thus children have rather chronic manic states characterized by severe irritability, 'affective storms', mood lability, severe temper outbursts, poor concentration, and impulsivity with or without clear episodicity.[19] There is a diurnal variation of mood, with such children difficult to rouse in the morning and gradually developing more overt irritability and hyperactivity by the evening. This has led to a re-categorization of many children previously diagnosed with the disruptive behaviour disorders of ADHD, oppositional-defiant disorder (ODD) and conduct disorder (CD). The 10-year review of paediatric BD in the *Journal of the American Academy of Child and Adolescent Psychiatry* (*JAACAP*) refers to this as the 'broad phenotype'.[20]

Wozniak describes high comorbidity of paediatric BD with ADHD (73% to 98% in the 12 years and under age group) and other psychiatric disorders of childhood. She reports ''the age of referral to our clinic is 8 years, about 75% of parents report symptoms beginning during the preschool years''.[21] Biederman *et al.* were able to recruit 31 preschoolers diagnosed with BD aged 4–6 years for an open label 8-week trial of risperidone versus olanzapine (but no placebo group) and conclude that both treatments resulted in a ''rapid reduction of symptoms of mania in preschool children''.[22] A marked rise in prolactin and weight occurred on both drugs.

The 'Narrow Phenotype'

The Geller *et al.* group in St Louis, in contrast, advocate for recognition of a 'narrow phenotype' that corresponds to the phenomenology described in the A criterion for DSM-IV, requiring elevated, grandiose or irritable mood and cycling with episodes of depression. However, Geller *et al.* argue for a radical shift in the time criteria and propose the concepts of 'complex cycling', 'ultrarapid cycling' (5–364 cycles per year) and 'ultradian cycling' (>365 cycles per year, cycle length of at least 4 hours duration).[23]

Geller *et al.* did much to first promulgate the idea of pre-pubertal BD in their 10-year review of the disorder in *JAACAP* in 1997.[24] In that seminal paper, Geller *et al.* posit that children and adolescents exhibit manic symptoms constrained by their developmental level. Thus, 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)'', and grandiose delusions by ''a manic adolescent, even in the absence of musical talent or ability to carry a tune, practising all day with the belief he or she can become a rock star'' etc.

The 10-year review by Pavuluri *et al.* in *JAACAP* in 2005[20] accepts validity of both 'narrow' and 'broad' phenotypes, and also an 'intermediate phenotype', and notes the National Institute of Mental Health (NIMH) research roundtable on pre-pubertal BD also accepts these concepts.[25] The Juvenile Bipolar Research Foundation in reference to a 2001 NIMH 'panel of experts' states ''new criteria for juvenile-onset bipolar disorder are being considered for DSM-V''[26]. However a conference in 2007[27] concluded further research of postulated phenotypes was necessary. According to Professor Leibenluft, chief, Section on Bipolar Spectrum Disorders at the NIMH, (Parry P, pers. comm, 2008) there has been ''definitely no agreement that they will be incorporated into DSM-V'' and it is ''premature to make any predictions'' as it is ''early in the DSM process.''

Acceptance of paediatric BD as a common condition with both 'broad' and 'narrow' phenotypes is made explicit in ''Treatment guidelines for children and adolescents with bipolar disorder'' by Kowatch *et al.*[28] The paper describes a comprehensive evaluation as interviewing preferably both parents and the child and optionally teachers, but notable by its absence is any description of play-based assessment for the child and it could be questioned why teacher interviews should not be mandatory in such an important diagnosis. Seven pages of pharmacotherapy guidelines follow, with a half page of psychosocial interventions focussing primarily on psychoeducation about BD.

DEBATE IN THE AMERICAN PSYCHIATRIC LITERATURE

Despite increasing acceptance of paediatric BD, there are sceptical voices in American psychiatry. Controversy hinges on several issues: whether pre-pubertal BD can even exist in that adolescent neurodevelopment may be a prerequisite for BD vulnerability; lack of prognostic predictability; lack of symptom specificity, and over-reliance on parental reports and checklists.

There is some neuroimaging evidence that BD may be like schizophrenia, a neurodevelopmental disorder and generally dependent on deviations from normal adolescent brain development.[29] Undoubtedly, cases are often missed early in their course until non-specific mood and behavioural symptoms in adolescence manifest more clearly as BD. However, this has to be balanced with the need to minimize false positive diagnoses. Retrospective studies in adults with BD have reported that up to 60% thought they experienced the onset of their BD before age 20 years and 10–20% reported onset before age 10 years,[30] and patients recalling pre-pubertal onset had a more severe course of their BD illness.[31]

However, most people can probably recall episodes of moodiness in their childhoods, and if one had developed BD later, then it could be natural to make an association with such childhood memories. Furthermore, 10–20% of 1% (if one accepts the adult prevalence rate of 1%) is much less than what is being suggested for childhood prevalence. Somewhat in contrast, an Australian prospective study of a clinical sample of 203 boys aged 9–13 years found 125 had ADHD and of these 25 met criteria for mania (broad phenotype), but 6 years later only one of the 25 boys could be said to have possible BD.[32] A review of follow-up studies concluded that ''there have been no observations of diagnosable BD in children under the age of 12 years''.[33]

In terms of scepticism about a diagnosis based on symptoms that traditionally have reflected other paediatric psychopathology, Harris,[34] a child psychiatrist, comments on her work in the Cambridge Hospital inpatient unit in Massachusetts, which is associated with the group of Biederman *et al*. There she found that one-quarter of the children aged 3–13 years in her care ''had been given a diagnosis of BD and were receiving mood stabilizers or antipsychotics'' and ''another quarter were believed to have bipolar disorder by their parents, who requested that appropriate medications be started''. She gives two case examples of children aged 10 and 11 years in the Massachusetts inpatient unit who responded to a careful history taking, re-diagnosis (one to autism, the other to PTSD), withdrawal of most medication and family-based therapy. Harris says that in her time on the inpatient unit, she thought perhaps only one pre-adolescent child (aged 12) truly had BD (Harris J, pers. comm., 2007). She adds:

> ''Many of the cases ... with a label of JBD (juvenile bipolar disorder) 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.''

The developmental perspective is stressed in a paper by Carlson and Meyer[35] that critiques the paediatric BD construct for being based excessively on cross-sectional symptom-based studies and needing a longitudinal developmental perspective.

These issues, including suggested over-reliance on parent questionnaires and structured interviews, have been vigorously debated in *JAACAP*.[36,37]

Critics of the diagnosis do not dispute that these children have severe emotional and behavioural problems. What they disagree with is use of the label of BD for these children.[35–37]

DEBATE IN THE AMERICAN PUBLIC MEDIA

The death in December 2006 of a 4-year-old girl who was on Quetiapine, Valproate and Clonidine[38] since being diagnosed with BD and ADHD at age 28 months has thrown the media spotlight onto the diagnosis. Issues of side-effects, including tardive dsykinesia,[39] possible other fatalities[40,41] and pharmaceutical company influence[42,43] have added fuel to an intense controversy that in the words of the New York Times on 4 September 2007 has "shaken child psychiatry".

INTERNATIONAL PERSPECTIVE

A review of the international literature suggests a very wide variation in rates of diagnosis of BD in the young adult age group.[44] Less is known of the paediatric age group, but the traditional view of BD being very rare prior to puberty appears prevalent outside the USA. This is not universal, however. Masi *et al.*[45] in Italy, Jairam *et al.*[46] in India, Maia *et al.*[47] in Brazil and Althoff *et al.*[48] in the Netherlands have found rates similar to American clinical cohorts, though by using a similar paradigm and methodology to either Geller's or Biederman's groups in the USA.

A pilot survey of Australian and New Zealand child and adolescent psychiatrists in December 2006[49] found a majority held to the traditional view that BD was very rare before puberty and uncommon in adolescence. The preliminary results from a larger follow-up survey supports these findings (Parry P et al., unpubl. data, 2008).

CONCLUSION

It remains to be seen where this trend will go in the USA and whether it will come to the Antipodes. A looming question for us in child and adolescent psychiatry is if for instance there were a shift in diagnostic criteria for DSM-V to encompass some of the postulated PBD phenoptypes, will traditional views and clinical practice drift in the American direction?

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CORRESPONDENCE

Paediatric bipolar disorder

DEAR SIR,

We thank Jairam for his thoughtful comment[1] on our paper concerning the controversy surrounding the diagnosis of paediatric bipolar disorder (PBD) especially among pre-pubertal children.[2] In response, we emphasize that the British National Institute for Health and Clinical Excellence (NICE) guidelines on bipolar disorder (BD) regard the bipolar spectrum in children as highly speculative and the case for inclusion in evidence-based practice remains unproven. They advocate caution until further research evidence becomes available.[3]

The main PBD hypotheses are that BD can be recognized reliably in childhood, and that early intervention will improve the course of the disorder. This line of research encounters the well recognized difficulty of long-term prediction in psychiatry, especially if using relatively frequent and non-specific symptoms to predict the emergence of uncommon conditions at a much later developmental stage. Jairam references Chang's paper, ''Adult bipolar disorder is continuous with paediatric bipolar disorder'',[4] which highlights the similar phenomenology between children and adults with BD. However, Chang's review in the *Canadian Journal of Psychiatry* was accompanied by a review by Duffy,[5] concluding there is no evidence of BD in pre-pubertal children. In particular, Duffy noted that in longitudinal studies of high-risk children of parents with well-characterized BD, ''there have been no observations of diagnosable BD in children under the age of 12 years''.

Alternative clinical hypotheses are evident in nearly all the studies of PBD, which has remarkably high levels of comorbidity; in fact, this is one of the most reproducible findings about the various childhood BD phenotypes.[6] These 'comorbidities' could be viewed as differential diagnoses and potential explanations for the mood dysregulation. For example, Rucklidge, in a ground breaking study of the psychosocial factors associated with a diagnosis of 'narrow phenotype' PBD in Christchurch,[7] found that over 50% had a history of trauma and that 21% met criteria for lifetime posttraumatic stress disorder (compared with 10% trauma exposure, 0% posttraumatic stress disorder among controls). Childhood trauma may well be implicated in these cases of mood dysregulation rather than PBD.

As NICE recommend, the threshold for a diagnosis of early-onset BD should be set particularly high as the implications are serious. PBD has been conceptualized as a life-long condition requiring long-term medical management beginning early in childhood. The risk of excessive pharmacotherapy, particularly in pre-pubertal children cannot be understated. In our paper,[2] we alluded to this with a reference to Wonodi *et al.*,[8] who examined 118 paediatric psychiatric patients aged 5–18 years on atypical antipsychotics for at least 6 months and found that 11 (9%) had tardive dyskinesia. There have been large numbers of fatalities relating to atypical antipsychotics[9] in the USA. The diagnosis of PBD is a major driving force for atypical antipsychotics being prescribed as long-term 'mood stabilizers' to children. Another aspect worthy of further discussion is the effect on a child's developing narrative of self and the meaning of their emotional life in the context of the PBD label.[10]

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Paediatric bipolar disorder

DEAR SIR,

In their recent publication, Parry and Allison set out to explore the rapid rise in the diagnosis of bipolar disorder in the paediatric, particularly pre-pubertal, age group in the USA over the past decade and to look at associated controversies.[1] It is important that clinicians in Australia have our own debate on this particularly important subject, and to do that we must be adequately informed and unbiased. It is not just an American phenomenon. The international literature[2–6] refutes the rise in diagnosis and highlights the need for clinical epidemiological reliability and diagnostic validity studies in view of the claims that paediatric bipolar disorder (PBD) carries high morbidity and psychosocial dysfunction because of its chronic and frequently rapid-cycling symptoms, high comorbidity with disruptive behaviour disorders and relative treatment resistance.[7–9] This is currently one of the most active and controversial areas of clinical and research interest in child psychiatry.

There seems a pervading sense of urgency in the US as public health implications of the increasing diagnosis of bipolar disorder affecting children and adolescents are publicized. Current literature depicts the disease as devastating, with substantial impairment across psychosocial domains, high risk of suicide, psychosis, significant familial aggregation, and protracted illness course in which the classically described cycles of disease followed by well periods are rarely observed.[10] Early recognition is called

doi: 10.1080/10398560802193161

for in both acute and maintenance treatment of bipolar spectrum disorders in children and adolescents in order to ameliorate ongoing symptoms and reduce or prevent serious psychosocial morbidity that usually accompanies this illness.[11]

The diagnosis of PBD poses problems as the diagnostic criteria are softened and radically inflated numbers result. Comorbidity reportedly between attention deficit hyperactivity disorder (ADHD) and bipolar disorder, oppositional defiant disorder (ODD), conduct disorder, posttraumatic stress disorder (PTSD) and other disorders of mood regulation are not considered and present enormous diagnostic and treatment challenges, evidenced by emerging reports that mania is being misdiagnosed as ADHD.[12] In children who present with both the DSM-IV and non-DSM-IV phenotypes, assessment should include careful evaluation and systematic monitoring of all abnormal behaviours to explore stability and change over time in diagnosis and impairment and medication used with the utmost responsibility. I would stress the complexities of making such a serious diagnosis at a stage of crucial development, in view of ''lack of maternal warmth'' being quoted by proponents of the PBD diagnosis in this age group as a predictor of faster relapse after recovery from mania[13] and in view of the role of the family in the onset and outcome of childhood disorders. Family dynamics are vitally important and there is a need to empirically assess which family processes are important for specific childhood disorders.[14] Discrepancies between reports of mother, child and father in childhood disorders are an inherent difficulty as sometimes parents are relieved when a diagnosis explains their concerns to date.

Research evidence is still unconvincing. The paediatric samples followed up have been of small to modest sizes, and subjects have been followed up infrequently or for relatively brief periods. So far, no study has prospectively collected syndromal and subsyndromal course data on children and adolescents representing the full spectrum of bipolar phenotypes, in particular bipolar disorder not otherwise specified.[15] Many children and adolescents cannot be meaningfully diagnosed using DSM-IV, and the variety of bipolar phenotypes observed in clinical practice remains unclarified.[8] Several research groups have published studies using semi-structured interviews to examine the cross-sectional presentation of bipolar 1 disorder in child and adolescent cohorts.

Traditional views have been shaped by the DSM, and PBD will be no exception. If DSM-V was to encompass some of the postulated PBD phenotypes, my major concern is that the role of developmental theory would take a backstage. Of further concern is that the symptom checklist type of diagnosis of PBD is dangerous, and so also is the recommended treatment, mainly because the symptoms can also be found in other disorders such as complex PTSD, ADHD and ODD, and the pharmacotherapy used in one may not be suitable for the other and in fact may be dangerous.

Has the relationship between the pharmaceutical industry, academic medicine and the national drug authorities affected the clinical practice of child psychiatry? ''Many leading researchers in this area,'' says Mary Burke, ''have financial relationships with the manufacturers of the drugs recommended for the treatment of PBD and although such relationships are not illegal, our credibility with the public is being jeopardized and constantly questioned''.[16] The reduction of child psychiatry to a biological model is in competition with those of us who espouse an integrated perspective of developmental psychopathology without blinding ourselves to the fact that some seriously disturbed children do require pharmacotherapy. The role of cumulative trauma, including attachment trauma in early life, the role of environmental stressors and family relationships cannot be disregarded. Yet, the biomedical model appears to be taking over and limiting treatment options available to psychiatrists. The bio-psycho-social model is dying. Psychiatry journals lately are full of multicolour scans and complex genetic maps indicative of the fantastic progress being made in understanding the biology of mental disorders. Actual human beings with mental disorders have practically disappeared from their pages. The patient is 'disappearing'[17] from psychiatry. Are we now running the risk of children and families 'disappearing' from child psychiatry?

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Paediatric bipolar disorder

DEAR SIR,

In his comment on the recent article by Parry and Allison,[1] Jairam mentions that paediatric bipolar disorder had been recognised 150 years ago by Esquirol.[2] This is somewhat misleading.

The first descriptions of what might now be called bipolar disorder in adults came from the 1850s. It was not until the end of the 19th century that manic depressive illness was outlined and not until the 1920s that the term came into widespread use for any age group.[3]

At the time Esquirol was writing, mania was a common term used for insanity in general, but despite this Esquirol did not use the term mania for the case to which Jairam refers. The case, which was that of an 8-year old boy, was described in a section headed 'Folie', an even more generic term for insanity, and was preceded by a statement that infancy is secure from insanity.[4]

The case that supposedly is a first description of paediatric bipolar disorder is as follows:

> "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." (p. 30)[4]

This is all the information Esquirol offers on this case. He gives no diagnosis. Elsewhere in the book, he picks out overactivity, disinhibition and loquacity as the leading features of hysteria. It would be interesting to obtain readers' formulations of this case.

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Acute trauma response at a conference abroad

DEAR SIR,

It is relatively uncommon for clinicians dealing with post-traumatic stress disorder (PTSD) to be called upon to use practice guidelines in an acute setting, given that it is unlikely that this type of practitioner would be present in a situation where the skills and knowledge can be directly applied in this context. We report the case of a traumatic incident affecting a large group of people, where recently released guidance[1] was utilized in a practical setting.

The Pharmaceutical Society of Australia regularly conducts off-shore educational events, and in 2007 a pre-conference seminar based in Morocco attracted 190 conference delegates. Early in the course of this event, an incident involving a violent attack by a mentally ill man resulted in the hospitalization of two members of the conference party in the city of Marrakech. As a result of machete wounds that included serious lacerations and fractures, these patients required an overnight stay in local hospital, sutures, intravenous antibiotics, CT scans, x-rays, and tetanus inoculations. Both were subsequently transported from Morocco for further treatment. A security guard from the hotel complex was also seriously injured. The assailant was alleged to have been an ex-employee of the resort hotel, said to have been recently released from a psychiatric hospital about 700 kilometres from the place of the attack. Considerable information detailing the attack was reported in Australian and other international media within hours of the event. Particularly in the period immediately after the attack, many of the people present were disturbed and unsettled by these events. At the time, a travel advisory from the Australian Department of Foreign Affairs and Trade suggested that Australians travelling to Morocco should exercise a high degree of caution because of a high threat of terrorist attacks against Western interests and recent suicide bombings, and some delegates were unsettled by the possibility that the attack might have been related to terrorism.

The conference organizers were in a unique position of coordinating a debriefing session provided by a speaker at the conference (LM). Prior to the session, which was attended by approximately 70 of the conference delegates, the Australian Centre for Posttraumatic Mental Health (ACPMH) guidelines for people exposed to traumatic events[1] were made available to all delegates. Given the proximity of the event to the release of the document, it is probable that this occasion was the first time that it had been used 'in the field' for a group of people affected by a traumatic event. The debriefing allowed the conference staff to provide clarification of the events surrounding the incident, as well as the opportunity to convey apologies and messages of empathy from various parties including the King of Morocco's delegation, the Mayor of Marrakech, the Moroccan Ministry of Tourism, the police, the manager of the hotel, and the conference staff. There was also discussion surrounding the role of the press. The session then focused on an exploration of the thoughts of the participants regarding the incident, discussing feelings such as anxiety and helplessness. The facilitator encouraged the participants to view the incident from a positive perspective, emphasizing strengths such as coping skills, supports and the sense of bonding that had emerged among those affected.

A feedback questionnaire was designed after detailed discussion with conference organizers, and the availability of the form was announced in a subsequent conference session. The voluntary nature of participation was stressed, and the questionnaire was copied by conference staff and left on

tables at tea breaks and lunchtime. Reponses received from 71 of approximately 190 delegates who had been on site in Marrakesh were completed 7–9 days after the incident. Twenty-five respondents described some form of first-hand relationship to the incident: 10 had arrived at the scene shortly afterwards, four respondents had arrived shortly afterwards and assisted, five reported that they had witnessed the incident first-hand, three provided personal assistance but not at the scene of the incident, and three responded that they had both witnessed the incident and provided personal assistance. The remaining 46 respondents reported that they had only heard about the incident afterwards. Descriptors most commonly selected by respondents were 'sad' ($n = 46$), 'anxious' ($n = 27$) and 'powerless' ($n = 21$). Younger respondents (aged < 60 years) were more likely to report feeling either fearful or helpless ($p < 0.001$ for each). Those with first-hand exposure to the incident were more likely to report that they felt 'panicky' than others who had heard about the event afterwards ($p < 0.05$). Self-help measures most often described as useful were 'talking with friends' ($n = 58$) and 'talking with the victims' ($n = 40$). In addition, 23 respondents described specific benefit from attending the debriefing session and 21 reported that they derived benefit from 'drawing on past experiences'. Most respondents reported that they expected "not to think about the incident very much at all in the future" ($n = 12$) or "I may think about the incidents from time to time but don't expect to be troubled by them" ($n = 57$). Three participants selected "I may think about the incidents from time to time and they may continue to upset me" and one respondent chose the alternative that specified "I may need to seek some form of help or counselling about the incident at some time". Several participants reported that the incident had prompted them to recall other previous traumatic events such as armed robberies of their pharmacies.

It is thought that this instance is the first time where the recently released ACPMH guidelines for helping others following frightening or distressing events have been used for a group of people in a practical setting. This report documents a unique first-hand perspective of trauma in an unfamiliar setting that resulted in an opportunity to counsel, assist victims and participants, and provide specialist advice to the conference organizers.

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The gain of suicide

DEAR SIR,

The recent publication, *The Loss of Sadness*,[1] helps to explain one of the discrepancies of suicide scholarship. In 1964, Stengel reported that 33.3% "of people who commit suicide have been suffering from a neurosis or psychosis or severe personality disorder".[2] Less than two decades later, Robins found mental disorder in 94% of patients who completed suicide;[3] that is, more than 2.5 times higher. Subsequent psychological autopsies (Robins' report was an early example) have supported this higher rate.

Robins[3] used the St Louis Suicide Study Criteria, which were closely related to the Feigner Criteria, which in turn, were a forerunner of the DSM criteria.

Horwitz and Wakefield are critical of the DSM criteria of major depressive disorder (MDD), stating that this a list of symptom which pays no heed to contextual matters (loss and other unwelcome events).[1] They state that the DSM MDD criteria lead to normal sadness being misdiagnosed as a disorder. They cite sociological studies that provide evidence that stressful events can result in features ('symptoms') that are indistinguishable from the DSM MDD criteria, but that when taken in context, these do not result in the diagnosis of MDD. Individuals who experience sad events may construe their symptoms as the natural reaction to their experience, may not consider themselves disordered and generally do not seek medical assistance.

The point we make is that the criticism made by Horwitz and Wakefield[1] can also be leveled at the diagnostic criteria used by Robins[3] because the St Louis Suicide Study Criteria and the Feigner Criteria are lists of symptoms with no contextual considerations.

Robins gives case vignettes of 63 people who were diagnosed with depression prior to suicide. Case 051 was a 61-year-old male who had been "a highly successful lawyer until a few months before his death". A long time gambler, he generated serious gambling debts. He embezzled money from his firm and was asked to resign. He was forced to sell his house but lost the proceeds gambling, and 1 week before his suicide he had to take his wife to live with their son. Case 056 was a 56-year-old man who had been living with a female partner for 20 years. She suffered a stroke and was moved to a nursing home 4 months before his suicide. "From the time the wife was taken away, he seemed totally lost and despondent and would ask his neighbors the same question over and over: 'What am I going to do?'". Case 075 was a single 86-year-old never married retired dentist. He was suffering "1) chronic asthmatic bronchitis, 2) prostatic hypertrophy, 3) hypotensive vascular heart disease, and 4) generalized arteriosclerosis". He had prostatic surgery. He developed a tumor under his nipple which was surgically removed 5 weeks before his suicide. The only time he mentioned "insomnia, anorexia and depression" was after his last discharge from hospital. Case 011 was a 57-year-old woman with rheumatic heart disease who had a foot severely crushed in an automobile accident. "The informant believed that the leg injury and the feeling of disgrace concerning her appearance and intelligence were the chief stresses that may have contributed to her suicide."

An older diagnostic system listed endogenous/biological depression and reactive depression. Endogenous depression was usually a severe depression, the hallmark feature being that it arose without external cause. Reactive depression was the depression which arose in the aftermath of an unwelcome event. The demarcation between normal sadness and reactive depression is indistinct and relies on the attitude of the 'patient' and the diagnostician.

In 1955, Sainsbury made a useful contribution.[4] He studied 390 suicides and concluded that mental disorder

was the principal factor in 37% of cases (similar to the 33.3% of Stengel) and a contributory factor in 47% of cases. The sum of these principal and contributory factors is 94% (exactly that of Robins).

When considering the role of mental disorder in suicide, it is important to think about primary and secondary categories, and to place cases in context. Psychiatry can be expected to do something about mental disorders, but little about most other aspects of life. A diagnostic system that acknowledges the importance of context would provide revised psychological autopsy outcomes.

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Jack Dale and Saxby Pridmore
Hobart, TAS

DSM-IV cure for post-traumatic stress disorder

DEAR SIR,

For those that struggle with the challenge of providing exposure therapies and other treatments for post-traumatic stress disorder (PTSD), there is good news. Medico-legal reports by learned colleagues have convinced me there is an easier remedy.

Let us take an uncomplicated case, say a horrific motor vehicle accident without physical injury or other ongoing stressor. When first assessed at say 9 months, PTSD is diagnosed and a suitable prognosis is proffered – full or partial but useful degrees of recovery are possible, but chronicity with a fluctuating course may yet ensue. It is too early to allocate an assessment of permanent psychiatric impairment. On review at 2 years, symptoms have moderated somewhat (at least at the time of the reassessment) and the DSM-IV PTSD criteria are no longer met. A diagnosis of an adjustment disorder with anxiety is allocated. Now here is the brilliance of the cure. The simple act of diagnosing an adjustment disorder (instead of PTSD in partial remission) means that the patient has to recover within at most 6 months and probably a lot sooner, as it is now some time since the original stressor. So zero impairment can be confidently assessed and there is no need for more of that troublesome exposure work, or any other treatment for that matter.

Importantly, for this cure to be effective in practice it is essential to wear a cross-sectional pair of spectacles – longitudinal ones don't work. It is also preferable not to have read conclusions that have been drawn from the Australian National Survey of Mental Health and Well-Being,[1] where the group in the population who have sub-syndromal symptoms were found to carry at least half the population burden of impaired mental health and social role performance.

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Chris Cantor
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Appendix A4

Child and Adolescent Mental Health
a journal for all professionals working with children and young people

Child and Adolescent Mental Health Volume 14, No. 3, 2009, pp. 140–147 doi: 10.1111/j.1475-3588.2008.00505.x

The Paediatric Bipolar Hypothesis: The View from Australia and New Zealand

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Background: The paediatric bipolar disorder (PBD) hypothesis arose in the USA and proposes childhood onset and high rates of prevalence. **Method:** Child and adolescent psychiatrists in Australia and New Zealand were surveyed about the PBD hypothesis. **Results:** Sixty percent responded (N = 199) and most (53%) reported never having diagnosed pre-pubertal PBD and a further 29% estimated seeing '1 or 2' cases. Most (83%) rated pre-pubertal PBD as 'very rare', 'rare' or 'not diagnosable'. Opinion varied as to whether PBD was over-diagnosed (25%), appropriately diagnosed (42%), or under-diagnosed (28%) in Australia and New Zealand, 5% were unsure. In contrast there was a consensus of views that PBD was over-diagnosed in the USA (90%), whilst less felt it appropriately diagnosed (3%), or under-diagnosed (1%) and 6% were unsure. **Conclusions:** The majority view was consistent with classical descriptions of bipolar disorder.

Key Practitioner Message:

- Paediatric bipolar disorder (PBD) as defined by USA researchers, applies to a range of child behavioural patterns that differ in varying degrees from traditional descriptions of bipolar disorder
- PBD has become a common diagnosis in the USA
- There is some evidence to suggest that adoption of the PBD diagnosis in the UK and Europe has been limited
- 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
- The PBD phenotypes remain hypothetical and the alternative hypothesis is that responses to trauma and other more recognised emotional and behavioural disorders of childhood remain sufficient diagnostic explanations

Keywords: Bipolar disorder; mania; diagnosis; emotion regulation; psychiatric practice

Introduction

Traditionally, bipolar affective disorder has been considered rare in children and uncommon in adolescence until typical onset in late adolescence or early adulthood. However paediatric bipolar disorder (PBD), sometimes termed 'juvenile bipolar disorder' or 'early onset bipolar disorder', has become a topical issue in child and adolescent psychiatry over the last decade, driven by research in the USA. The proponents of PBD are concerned that the traditional approach to bipolar disorder in children and adolescents (where bipolar disorder is considered rare in pre-pubertal children) is missing a large number of distressed children, whose course of bipolar illness could be ameliorated or attenuated by early treatment.

While PBD has been the focus of a great deal of interesting research, especially around phenomenology, it remains largely a hypothetical disorder and has yet to gain the robust evidence required for routine clinical treatment (Parsonage & Hinds, 2008), specifically:

1. bipolar disorder prodromes cannot be reliably detected in childhood and shown to progress to established bipolar disorder in adulthood;
2. early intervention, usually mood stabilisers, has not been demonstrated as safe and effective for children with these early onset states;
3. early intervention, for instance prophylactic medication given in childhood, has not yet been shown to improve the long-term outcomes for adult bipolar disorder.

This paper explores the extent to which the 'PBD hypothesis' has permeated child and adolescent psychiatry practice in Australia and New Zealand, with comparison to the USA, the UK and Europe.

PBD in the USA

Clinically, PBD has become a much more common diagnosis in the USA since the mid-1990s. For instance,

Conflict of interest statement: Dr Parry is a member of a medical/pharmacy non-government organisation: 'Healthy Skepticism' (see: http://www.healthyskepticism.org). Dr Furber and Dr Allison have no conflict of interest to declare.

Published by Blackwell Publishing, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main Street, Malden, MA 02148, USA

the number of visits to primary care physicians in the under 20 age group where the diagnosis was bipolar disorder increased from 0.01% in 1994/5 to 0.44% in 2002/3 (Moreno et al., 2007) and according to data from the Centre for Disease Control, bipolar disorder has become the most common diagnosis in children under age 12 receiving psychiatric hospitalisations (Blader & Carlson, 2007). The USA has also witnessed a significant rise in popularity of the diagnosis in the media with several consumer organisations now promoting the diagnosis of 'bipolar children' (Parry & Allison, 2008).

This extraordinary rise in diagnosis and acceptance of PBD in the USA appears related to shifts in criteria and conceptualisation of bipolar disorder as it presents in the paediatric age group, led by work in several academic centres of child psychiatry. This exploratory search for hypothetical bipolar disorder prodromes in childhood represents the main area of activity in PBD research so far. In St Louis, Missouri, Geller and Luby (1997) conceptualise a 'narrow phenotype' that includes classical DSM-IV mania or hypomania features but 'constrained by developmental level' and permitting much more liberal time criteria such as ultradian cycling (more than one mood shift per day) and continuous cycling or chronic manic states. In Boston, Massachusetts, Biederman (1998) and Wozniak (2005) conceptualise a 'broad phenotype' where the cardinal feature of paediatric mania is irritability, not requiring elevated or euphoric mood, thus many children previously diagnosed with ADHD, oppositional-defiant disorder and conduct disorder are re-diagnosed as suffering bipolar disorder. In Ohio, Kowatch et al. (2005) and Findling et al. (2001) endorse both phenotypes and have been instrumental in promulgating treatment guidelines. Such is the research interest in these criteria shifts, the US National Institute for Mental Health (NIMH [2001]) 'research roundtable on pre-pubertal bipolar disorder' now accepts the new expanded phenotypes for research (Parry & Allison, 2008).

PBD in the UK and Europe

In the UK and Europe, existing epidemiological data and clinical practice guidelines are consistent with the classical diagnostic approach and suggest bipolar disorder in the paediatric age group is very rare, with pre-pubertal PBD virtually non-existent. Unlike in the USA, inpatient units in the UK and Denmark have rarely diagnosed mania or bipolar disorder. Sigurdsson et al. (1999) in a 22 year retrospective study at the Maudsley, defined only 38 cases of either bipolar disorder or psychotic depression, with mean age of 14.2 years (range 11 to 18 years). Anecdotally Soutullo et al. (2005) reported that none of the 2,500 children 10 years or younger referred to the Royal Manchester Children's Hospital University Department of Child and Adolescent Psychiatry had a diagnosis of mania or bipolar disorder. In Denmark, only 39 cases (1.2%) of psychiatrically hospitalised children aged 15 and under between 1970 and 1986 were diagnosed with bipolar disorder (Thomsen et al., 1992). A more recent German survey (Meyer, Koßmann-Böhm, & Schlottke, 2004) revealed German child and adolescent psychiatrists were largely holding to a traditional stance as only 8% claimed to have diagnosed a pre-pubertal child with bipolar disorder.

The classical diagnostic approach is also captured in the British National Institute for Health and Clinical Excellence (NICE) guidelines on bipolar disorder (NICE, 2006) which states that pre-pubertal bipolar disorder is 'very rare' and adolescent bipolar disorder is 'rare'. They advocate for strict use of Bipolar-I disorder criteria as per DSM-IV and ICD-10 and state that Bipolar-II disorder diagnosis should not be made except perhaps in older developmentally mature adolescents. Irritability as a core criterion (as it is in the 'broad phenotype') is specifically excluded. The guidelines discuss use of Bipolar-II and Bipolar disorder-Not Otherwise Specified 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). The NICE guidelines highlight the problems of lack of symptom specificity during development and that other diagnoses and environmental factors including abuse should be considered first. They caution against use of rating instruments such as the Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS: [Geller et al., 1996]), which are popular in the American academic literature, for diagnosing PBD in the absence of an extensive clinical assessment.

One of the main postulated lines of evidence for the PBD hypothesis is the retrospective recall of age of onset by adult patients with bipolar disorder. However these studies can also be affected by diagnostic bias. In a recent paper of retrospective accounts by adults with bipolar disorder, Post et al. (2008) found a German and Dutch cohort to have a much later remembered age of onset to an American cohort. The two cohorts differed on phenomenology: the Europeans were more likely to have had psychosis and the USA sample having a mix of rapid-cycling, dysphoric mania, abuse and trauma histories. The more classic bipolar disorder group remembered a later age of (and European) onset.

PBD in Australia and New Zealand

One of the current authors (PP) first became aware of the American PBD issue from a presentation on the topic (Healy, 2006). Subsequent discussion with colleagues in child and adolescent psychiatry in South Australia suggested few were aware of American PBD diagnostic practices and were very surprised upon hearing of them. In contrast to the USA where the diagnosis of PBD has been widely debated in the public media, the Australian and New Zealand (ANZ) media has been almost silent. Anecdotally it is only recently that parents have been asking child psychiatrists, paediatricians and Child and Adolescent Mental Health Service (CAMHS) clinics, the question: 'could it be bipolar?'

As far as the authors are aware, PBD made its first academic appearance at the Faculty of Child and Adolescent Psychiatry of the Royal Australian and New Zealand College of Psychiatrists (FCAP of the RANZCP) annual meeting in Darwin in 2004 (Birmaher, 2004).

A full symposium at the RANZCP Congress in May 2007 was cautiously favourable to the expanded American diagnostic phenotypes (Hazell et al., 2007). This symposium was repeated at the FCAP annual meeting in October 2007 where a more sceptical view was also presented (Parry, 2007a).

In Australia and New Zealand perhaps the first journal paper to allude to the PBD hypothesis was in the *Medical Journal of Australia* (Berk et al., 2006). Conversely, Berk et al. (2007) in the same journal, whilst advocating for early intervention for adolescents and young adults where 'mania is often atypical, mixed or dysphoric', do not specifically refer to or appear to endorse the American expanded PBD phenotypes.

The first paper devoted to PBD diagnostic criteria was a paper in the *Australian and New Zealand Journal of Psychiatry* by Cahill et al. (2007), who favoured using the more broad American NIMH guidelines to set the diagnostic threshold, but apply aspects of the much more stringent British NICE guidelines in the process of assessment and follow-up. This was followed by a guest editorial in the *ANZJP* encouraging early intervention for 'early onset bipolar disorder' (Mao & Findling, 2007). The Mao and Findling editorial drew two sceptical responses, from Parry et al. (2008) and Parsonage & Hinds (2008), and two of the current authors published a review in *Australasian Psychiatry* (Parry & Allison, 2008). Otherwise, papers referring to bipolar disorder criteria, particularly in the adolescent age range, have utilised traditional criteria (McShane et al., 2006).

Of ANZ child and adolescent psychiatrists publishing in the international literature, Hazell and colleagues from New South Wales, Australia, published in the *Journal of the American Academy of Child and Adolescent Psychiatry* (JAACAP) a follow-up study of 125 boys aged 9 to 13 with ADHD of whom 25 met criteria for 'broad phenotype' mania. Six years later, only 1 of the 25 boys could be said to have possible BD (Hazell et al., 2003). Rucklidge (2006) from New Zealand published in the *Journal of Affective Disorders* a study linking higher rates of trauma and poorer coping skills in adolescents who met DSM-IV Bipolar-I disorder, Bipolar-II disorder or Bipolar-Not Otherwise Specified (predominantly 'narrow' phenotype) criteria, compared to a control group. Finally, Werry, of Auckland, New Zealand has published in the JAACAP (Werry, McClellan, & Chard, 1991; Werry & McClellan, 1992) on early onset bipolar disorder but emphasising a more evidence-based interpretation of bipolar disorder as a rare disorder with a tendency to late adolescent onset.

In 2006, (PP) organised a pilot email survey of opinions of fellows of the FCAP of the RANZCP on the PBD issue, the results of which were published in the FCAP of the RANZCP e-Bulletin (Parry, 2007b). Responses indicated a passionate divergence of views on this important issue and the need for a more robust survey. In light of the results of this preliminary survey, the marked differences between the USA and UK/Europe in terms of the permeation of the 'PBD hypothesis' and the emerging dialogue in Australia/ New Zealand, this study sought to survey the viewpoint and practice of ANZ child and adolescent psychiatrists with regards to PBD.

Method

Participants

Participants were 199 child and adolescent psychiatrists in Australia and New Zealand. Of these, 195 were fellows of the FCAP of RANZCP and were self-selected from a total of 328 fellows approached via post and email, a return rate of 60%. The additional four participants were child and adolescent psychiatrists, retired or visiting locum, who completed the survey while at the annual FCAP conference.

Materials

The survey (see Appendix 1) was developed in print and electronic versions. The print version was posted to participants while the electronic version was set up online at http://*www.surveymonkey.com*. The survey was designed to cover a range of topics from psychiatric experience to opinions regarding the prevalence and aetiology of child and adolescent bipolar disorder while being quick to complete.

Procedure

The survey was approved by Flinders Clinical Research Ethics Committee of Southern Adelaide Health Service/ Flinders University. The survey period ran from mid-September 2007 to mid-November 2007. A four-stage survey collection procedure involving de-identification of survey responses was used to ensure confidentiality and maximise return rate:

Stage 1: Mail-out #1. The investigators provided the FCAP secretariat with enough surveys and envelopes to mail out to all 328 FCAP fellows. The FCAP secretariat produced a master list of fellows and assigned unique ID codes (i.e., coded 1–328). The survey was mailed along with an information sheet and return envelope, addressed to author GF. Both the return envelope and survey included the individual's unique identifier. Participants were informed they could choose to complete the survey online.

Stage 2: Mail-out #2. Following the first mail-out, GF provided the FCAP secretariat with the ID codes returned (print and online). The secretariat marked these individuals off the master list and organised a second mail-out to participants who had not yet responded.

Stage 3: Conference ballot box. At the annual FCAP conference, a ballot box was set up so members could complete the survey and submit it, with their details, to the FCAP secretariat. After the conference, the secretariat removed identifying details from the survey envelopes, applied the ID code and forwarded the surveys to GF.

Stage 4: Reminder in FCAP newsletter and email reminder. The final stage of data collection involved an advertisement in the FCAP newsletter requesting members to complete the survey if they had not already done so. Members who had provided email contact details to the FCAP secretariat were also sent a reminder email.

Data analysis

Quantitative data was collated into SPSS (version 14.0) for descriptive analysis. Missing data was excluded on an item-by-item basis. Where two or more surveys with

the same ID code were received, the most recent survey was included.

Results

Participant characteristics

A total of 199 psychiatrists (111 male and 87 female) returned the survey. The majority (184) completed the written survey while 15 completed the web-based version. Six respondents indicated they were no longer practicing clinically, of whom three only completed the participant characteristics. Five respondents returned two surveys, as identified through the ID code. In all five cases, the second survey was used. In total 199 surveys were available for analysis, of which 196 had (with the exception of the occasional item) the full complement of data. Table 1 summarises the characteristics of the 199 participants in terms of age, average years of child and adolescent psychiatry (CAP) experience, and average CAP inpatient experience.

Consistent with the sample being primarily fellows of the FCAP of RANZCP, when workloads were averaged, the majority of the work was being done with children and adolescents (79%) versus work with adults (21%).

Estimation of number of BD cases seen - lifetime

Estimates of the number of cases of bipolar disorder (BD) seen in pre-pubertal, post-pubertal and adult populations are summarised in Table 2.

The majority of participants (53.4%) said they had never seen a case of pre-pubertal bipolar disorder, whilst a further 28.5% estimated they'd seen only '1 or 2' cases. Only 35 participants (18.2%) estimated having seen 3 or more cases of pre-pubertal bipolar disorder. The spread of responses was different for adolescent cases. The majority of participants (96.4%) reported having seen at least one case of post-pubertal bipolar disorder and 124 (63.9%) estimated having seen more than half a dozen cases. Consistent with participants working primarily in child and adolescent settings, there was a significant number (20.9%) who had never seen a case of adult bipolar disorder. The biggest number however, 80 (42.8%) had seen more than 15 cases of adult bipolar disorder. These results suggest that ANZ child and adolescent psychiatrists are seeing quantitatively different rates of bipolar disorder in pre-pubertal children compared to post-pubertal adolescents and adults.

Estimation of number of BD cases seen - previous 12 months

Participants' estimates of the number of cases of bipolar disorder they had seen in the last 12 months in pre-pubertal, post-pubertal (i.e., adolescent) and adult populations are summarised in Table 3.

Only 24 (12.2%) participants had seen a case of pre-pubertal bipolar disorder in the last 12 months compared with the 110 (56.1%) who had seen 1 or more cases of post-pubertal bipolar disorder and the 86 (45.7%) who had seen 1 or more cases of adult bipolar disorder. These results further confirmed that in practice, child and adolescent psychiatrists are seeing considerably fewer cases of pre-pubertal bipolar disorder compared to post-pubertal and adult cases.

Opinions on prevalence of bipolar disorder

Participant's opinions regarding the prevalence of bipolar disorder in pre-pubertal and post-pubertal populations are summarised in Table 4.

Opinions regarding prevalence rates mirrored cases seen. Most participants (83.1%) were of the opinion that bipolar disorder in pre-pubertal children was either 'very rare (<0.01%)', 'rare (<0.1%)' or 'cannot be diagnosed' in this age group. Only one participant thought the disorder was 'common (0.5 to 3%)' and no-one thought it 'very common'. In contrast, participants viewed bipolar disorder as more prevalent in the adolescent age group with the largest proportion of participants (57.1%) rating post-pubertal bipolar disorder as

Table 1. Participant characteristics

Characteristic	*N*	*M*	*SD*	Range
Age				
40 years or less	33 (16.6%)			
41–60 years	135 (67.8%)			
60 years +	31 (15.6%)			
CAP experience (years)	198	15.09	9.57	2–40
CAP inpatient experience (years)	197	4.11	5.10	0–25

Table 2. Estimates of numbers of cases of BD ever seen

Estimated number of BD cases seen:	Pre-pubertal children		Post-pubertal < age 18		Over 18 years age	
	n	% (valid %[1])	*n*	% (valid %[1])	*n*	% (valid %[1])
Nil	103	51.8 (53.4)	7	3.5 (3.6)	39	19.6 (20.9)
1 or 2	55	27.6 (28.5)	18	9.0 (9.3)	11	5.5 (5.9)
3 to 5	16	8.0 (8.3)	45	22.6 (23.2)	28	14.1 (15.0)
6 to 10	6	3.0 (3.1)	44	22.1 (22.7)	17	8.5 (9.1)
11 to 15	9	4.5 (4.7)	22	11.1 (11.3)	12	6.0 (6.4)
>15	4	2.0 (2.1)	58	29.1 (29.9)	80	40.2 (42.8)
Did not answer	6	3.0	5	2.5	12	6

[1]valid % excludes missing data (i.e. those participants who did not respond)

Table 3. Estimates of numbers of cases of BD seen in last 12 months

Estimated number of BD cases seen:	Pre-pubertal children		Post-pubertal < age 18		Over 18 years age	
	n	% (valid %[1])	*n*	% (valid %[1])	*n*	% (valid %[1])
Nil	172	86.4 (87.8)	86	43.2 (43.9)	102	51.3 (54.3)
1	14	7.0 (7.1)	31	15.6 (15.8)	23	11.6 (12.2)
2	3	1.5 (1.5)	26	13.1 (13.3)	18	9.0 (9.6)
3 to 5	5	2.5 (2.6)	31	15.6 (15.8)	14	7.0 (7.4)
>5	2	1.0 (1.0)	22	11.1 (11.2)	31	15.6 (16.5)
Did not answer	3	1.5	3	1.5	11	5.5

[1]valid % excludes missing data (i.e. those participants who did not respond)

'uncommon', the next largest as 'common' (20.9%), followed by 19.9% seeing it as a 'rare' disorder.

Opinions regarding diagnosis of PBD in Australia/ New Zealand and the USA

Participants' opinions regarding diagnosis of PBD in Australia/ New Zealand, compared to the USA, are summarised in Table 5.

Participants varied in their opinions regarding diagnosis of PBD in Australia and New Zealand. While a sizable minority (42.3%) reported that PBD was 'appropriately diagnosed', there was evidence of two significant groups with opposite opinions. Fifty-five clinicians (28%) rated PBD as 'very' or 'somewhat under-diagnosed' and 48 (24.5%) clinicians who rated PBD as 'very' or 'somewhat over-diagnosed'.

In contrast, there was a clear trend towards identifying PBD as being over-diagnosed in the USA with 177 participants (90.3%) reporting they believed PBD was 'somewhat' or 'very over-diagnosed' in the USA. These results suggest that while there is some debate as to diagnosis rates in Australia and New Zealand, there appears to be a consensus that diagnosis rates of PBD in the USA are excessive.

Table 4. Opinion on prevalence of BD in pre-pubertal children and post-pubertal adolescents

	In pre-pubertal children		In post-pubertal adolescents	
BD is:	*n*	% of answers (valid %[1])	*n*	% of answers (valid %[1])
Very rare (<0.01%)	100	50.3 (51.0)	3	1.5 (1.5)
Rare (<0.1%)	59	29.6 (30.1)	39	19.6 (19.9)
Uncommon (0.1 to 0.5%)	32	16.1 (16.3)	112	56.3 (57.1)
Common (0.5 to 3%)	1	0.5 (0.5)	41	20.6 (20.9)
Very common (3 to 5% or more)	0	0.0	1	0.5 (0.5)
Do not think BD can be diagnosed in this group	4	2.0 (2.0)	n/a	0.0
Did not answer	3	1.5	3	1.5

[1]valid % excludes missing data (i.e. those participants who did not respond)

Table 5. Opinions on rates of diagnosis in Australia/ New Zealand and USA

	In Australia/ New Zealand		In the USA	
BD:	*n*	% of answers (valid %[1])	*n*	% of answers (valid %[1])
Very underdiagnosed	12	6.0 (6.1)	0	0.0
Somewhat underdiagnosed	43	21.6 (21.9)	2	1.0 (1.0)
Appropriately diagnosed	83	41.7 (42.3)	5	2.5 (2.6)
Somewhat overdiagnosed	41	20.6 (20.9)	53	26.6 (27.0)
Very overdiagnosed	7	3.5 (3.6)	124	62.3 (63.3)
Unsure	10	5.0 (5.1)	12	6.0 (6.1)
Did not answer	3	1.5	3	1.5

[1]valid % excludes missing data (i.e. those participants who did not respond)

Opinions regarding comorbidity, switching, activation, alternative diagnoses and upcoding in PBD

Participant's responses to questions examining key issues in PBD are summarised in Table 6. Three of the five questions showed strong trends. The majority of participants (78.5%) did not agree that in Australia and New Zealand other diagnoses (ADHD, Anxiety, Adjustment, PTSD, parent-child problems, peer relationship

Table 6. Comorbidity, switching, activation, alternative diagnosis and upcoding in PBD

	n	% of answers	Valid %
A significant proportion of other diagnoses (e.g. ADHD, anxiety, adjustment disorders, PTSD, parent-child problems, peer relationship problems) in Australia and New Zealand should in fact be diagnosed as PBD			
Strongly agree	8	4.0	4.1
Agree	17	8.5	8.7
Neutral	12	6.0	6.2
Disagree	46	23.1	23.6
Strongly disagree	107	53.8	54.9
Unsure	5	2.5	2.6
Did not answer	4	2.0	
Manic switching when taking antidepressants probably explains many of the cases of PBD in the USA			
Strongly agree	6	3.0	3.1
Agree	33	16.6	16.8
Neutral	53	26.6	27.0
Disagree	52	26.1	26.5
Strongly disagree	12	6.0	6.1
Unsure	40	20.1	20.4
Did not answer	3	1.5	
The *activation syndrome* from SSRIs probably explains many of the cases of PBD in the USA			
Strongly agree	5	2.5	2.6
Agree	40	20.1	20.4
Neutral	59	29.6	30.1
Disagree	42	21.1	21.4
Strongly disagree	10	5.0	5.1
Unsure	40	20.1	20.4
Did not answer	3	1.5	
Other diagnoses (e.g. ADHD, anxiety, adjustment disorders, PTSD, parent-child problems, peer relationship problems) probably explain many of the cases of PBD in the USA			
Strongly agree	64	32.2	32.7
Agree	102	51.3	52.0
Neutral	15	7.5	7.7
Disagree	4	2.0	2.0
Strongly disagree	1	.5	.5
Unsure	10	5.0	5.1
Did not answer	3	1.5	
Diagnosis upcoding to gain increased funding for therapy probably explains many of the cases of PBD in the USA			
Strongly agree	39	19.6	19.9
Agree	65	32.7	33.2
Neutral	36	18.1	18.4
Disagree	2	1.0	1.0
Strongly disagree	1	.5	.5
Unsure	53	26.6	27.0
Did not answer	3	1.5	

[1]valid % excludes participants who did not answer

problems) should be diagnosed as PBD, suggesting PBD was not seen as a more accurate or useful diagnosis for common presentations. Similarly, 84.7% of participants 'agreed' or 'strongly agreed' that these other diagnoses probably explained many of the cases of PBD in the USA. Over half of participants (53.1%) agreed that 'diagnostic upcoding' for increased funding explained many of the cases of PBD in the USA. However a significant number were 'unsure' (27.0%) or 'neutral' (18.4%), suggesting a lack of knowledge of the American health system.

There was considerable variation and uncertainty in opinions in relation to whether 'manic switching' or the 'activation syndrome' could account for many cases of PBD in the USA.

Discussion

This is the first large scale bi-national survey of child and adolescent psychiatrists' opinions and diagnostic practice regarding PBD in Australia and New Zealand. It comes at a critical time when the international debate over PBD is increasing in intensity and provides a snapshot of how ANZ psychiatrists are reacting to the initial stages of this contest of ideas.

'*PBD hypothesis*' *in Australia & New Zealand*

There are currently no accepted guidelines for the diagnosis and treatment of PBD in Australia and New Zealand and little information is available on child and adolescent psychiatrists' clinical practice with PBD. In this context a new urgency has entered the discussion of PBD with calls for the immediate adoption of the new broader US criteria for clinical practice in Australia and New Zealand (Cahill et al., 2007).

The results of this survey however, suggest that ANZ child and adolescent psychiatrists remain solidly sceptical of the American PBD phenotypes ('PBD hypothesis') with 90% believing that PBD is over-diagnosed in the USA. The majority (83%) was of the opinion that pre-pubertal PBD is a condition that is rare, very rare or undiagnosable. Given this majority opinion, most ANZ child and adolescent psychiatrists (86%) had not diagnosed a pre-pubertal case in the past 12 months, with 7% seeing a single case and only 5% seeing more than one case (this represented 10 psychiatrists among the entire sample). Just over half of the respondents (53%) had never diagnosed a case of PBD in a pre-pubertal child in their professional life with a further 27% estimating that they have seen only 1 or 2 cases.

Whilst on the whole, the results of the current survey suggest scepticism about the 'PBD hypothesis', there is evidence that views may have shifted, or may shift around this issue. Although 42% thought current diagnostic practices appropriate, more psychiatrists were dissatisfied with the status quo with about equal proportions having opposing views about whether PBD was under-diagnosed in ANZ (28%) or over-diagnosed (25%). Thus there are substantial numbers of respondents who could be influenced either way by evidence emerging from studies of the main research hypotheses. These numbers are consistent with the 21% of respondents in the pilot survey (conducted 10 months previously) who reported they saw PBD as more common than they used to. This could reflect changing views amongst a proportion of ANZ child and adolescent psychiatrists due to exposure to information about the new American phenotypes of PBD. Certainly in the months leading up to the survey there had been papers in the local literature (Cahill et al., 2007; Mao & Findling, 2007) and a symposium (Hazell et al., 2007) at the RANZCP Congress in May 2007, all of which raised awareness of the PBD concept amongst ANZ psychiatrists.

The alternative hypotheses

Most psychiatrists in this ANZ survey (79%) indicated that categories such as ADHD, anxiety, adjustment disorders, post-traumatic stress disorder (PTSD), parent-child problems and peer relationship problems were valid and could not be better accounted for by the PBD hypothesis. Hence most psychiatrists seemed to be sticking with established diagnoses and the substantial evidence base for treating these conditions.

These more established diagnoses are often termed co-morbidities in the PBD literature. PBD is well recognised as having remarkably high levels of overlap with a range of internalising and externalising disorders, in fact this is one of the clearest findings about the PBD phenotypes (Wozniak et al., 2004). As PBD is a hypothetical construct at this stage, it may be better practice to focus on these more established conditions as ANZ child and adolescent psychiatrists seem to be doing.

Further exploration of the diagnostic overlap could assist in understanding the mood lability that is being characterised as PBD. For instance in one of the few studies of the psychosocial difficulties associated with PBD, Rucklidge (2006) found that over 50% had a history of trauma compared with only 10% of the normal control group; 21% of the PBD group met criteria for lifetime PTSD whilst none of the control group did. Trauma can be a cause of mood dysregulation and clinically, it could be more reasonable to interpret the mood lability as secondary to trauma rather than infer it is early manifestations of a bipolar disorder, particularly if the full DSM-IV Bipolar-I disorder criteria are not being met.

Child and adolescent psychiatrists in Australia and New Zealand tended to agree with this position with 85% believing other common diagnoses such as PTSD probably explain many of the cases of PBD in the USA. Fifty three percent thought that 'diagnosis upcoding' could be encouraging this process in the USA. Diagnostic upcoding is the practice of giving a more serious diagnosis in order to access funding for therapy or hospital admission and has been raised in relation to rising rates of PBD (Blader & Carlson, 2007).

International perspective

This scepticism is certainly consistent with trends noted in the UK and Europe. Although to our knowledge no comparable survey of child and adolescent psychiatrists has been conducted in the UK, the NICE guidelines reflect the classical approach and are in accordance with earlier epidemiological data from the UK that found bipolar disorder to be a very rare disorder in the paediatric age group and almost non-existent pre-puberty. Notably, the NICE criteria state that for a child to achieve a Bipolar-I disorder diagnosis, they

would need to demonstrate 'elevated or euphoric mood for most of the time on most days for seven consecutive days' and following an episodic course. This would rule out most of the cases diagnosed with the proposed USA criteria.

The German survey conducted in 2002 (Meyer et al., 2004) showed German child and adolescent psychiatrists were even more conservative in their diagnosing practices than ANZ child and adolescent psychiatrists. Ninety two percent of their sample had never diagnosed a pre-pubertal child compared with the 53% of ANZ psychiatrists in our study. For the adolescent age group, 37% of German psychiatrists had never diagnosed bipolar disorder compared with 3.6% of ANZ psychiatrists. However it should be noted that Meyer et al. (2004) surveyed only those working in outpatient clinics, whereas the ANZ sample included inpatient psychiatrists and this could have influenced results.

Interestingly, the authors of the German survey referenced the American literature on PBD and expressed concern about potential under-diagnosis of PBD. They also noted that during their study they 'repeatedly got calls from psychiatrists who expressed some hesitance to use diagnostic categories such as bipolar disorder for young patients because of possible adverse long-term effects and stigmatisation' (Meyer et al., 2004) A more recent German paper (Holtmann et al., 2007) found similar rates of PBD phenotypes to USA research by using similar methodology based on the PBD version of the Child Behaviour Checklist (CBCL-PBD). Although noting that cases found may lack validity and not be 'real PBD', they advocate for use of the PBD phenotypes at least to identify a group of disturbed children and adolescents.

Status of the PBD hypothesis

Proponents of the PBD diagnosis are concerned with the traditional approach favoured by most of the psychiatrists in this survey (Biederman, 2003; Mao & Findling, 2007; Kowatch, 1998; Birmaher & Axelson, 2006). They argue the potential good of treating large numbers of children and adolescents, all of whom are distressed, and presume continuity with adult bipolar disorder (Chang 2007). Despite this, PBD remains a hypothetical disorder and as the NICE guidelines highlight, although various phenotypes have been described, follow up studies to adulthood have not been completed and considerable further studies using randomised controlled trials are required to show the safety and effectiveness of adult bipolar medication with children. Finally longitudinal studies of the long term outcomes of mood stabilisers on the course of the disorder are needed.

Given the infancy of these lines of research there is a strong case for caution until more conclusive evidence becomes available. So following a practice of evidence-based medicine, most ANZ child and adolescent psychiatrists seem to be wisely cautious and awaiting the evidence. Essentially, PBD remains a hypothetical disorder requiring further investigation to determine whether it can be incorporated into evidence based practice.

Limitations of this survey

Several limitations to the study need to be acknowledged. The response rate of 60% is respectable for a professional survey but very little information is available about non-respondents. Secondly the study relied on self report and there was no independent data to estimate the 'true' rates of PBD diagnosis. It is reasonably clear that the respondents used the diagnosis infrequently, however there was no objective gold standard to determine if these rates indicate accurate diagnosis or not. Obviously the diagnostic criteria used for the gold standard would greatly affect the rates of diagnosis.

Conclusion

The majority of ANZ child and adolescent psychiatrists report diagnosing PBD rarely and cautiously and appear not to have changed their diagnostic practice to any substantial extent. Most believe that more established diagnoses better explain the cases they see and possibly the cases in the USA who are diagnosed with PBD.

There is a divergence of views for and against the PBD hypothesis with substantial groups believing the condition is either under-diagnosed or alternatively over-diagnosed in Australia and New Zealand. Time will tell if views change as more evidence emerges on the key PBD hypotheses. The results of this survey are important as they confirm the caution ANZ child and adolescent psychiatrists have towards this new diagnosis and suggest that future treatment guidelines for PBD need to be firmly based on the evidence.

Acknowledgements

The survey was conducted with the approval of the executive of the FCAP of the RANZCP. The authors express their gratitude to Ms Joelle Lasserre and Ms Jennifer O'Donnell-Pirisi, membership administrative officers at the RANZCP, and Mr Jon Cullum for their very valuable assistance with the survey.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1: PBD Survey Questions.

Appendix S2: Information sheet accompanying first mailout.

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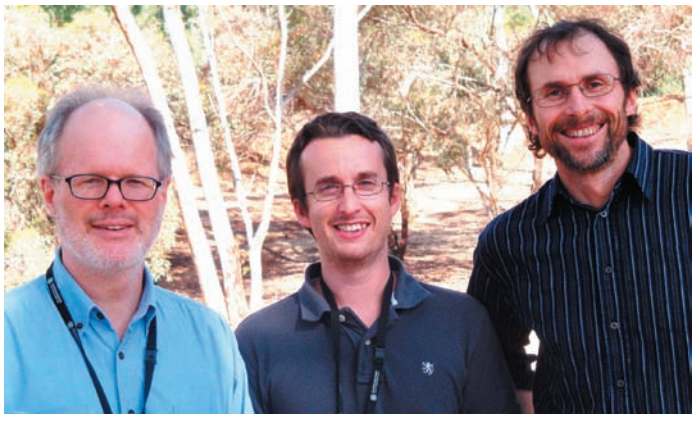
Results of the Survey of Faculty of Child & Adolescent Psychiatry Members' Views of Paediatric Bipolar Disorder

Members of the Faculty may recall a survey of their views of paediatric bipolar disorder (BD) that ran from mid-September to mid-November 2007. 199 members of the Faculty responded, a response rate of 60%. Mean length of Child & Adolescent Psychiatry experience was 15 years. Although results of the 16 item questionnaire have been published in the journal Child and Adolescent Mental Health http://www3.interscience.wiley.com.proxy.library.adelaide.edu.au/journal/121428024/abstract as "The paediatric bipolar hypothesis: the view from Australia and New Zealand," these results are published in the Bulletin to ensure that all Faculty members receive feedback. Your assistance in this project is much appreciated.



From left, Steve Allison, Gareth Furber, and Peter Parry outside Flinders Medical Centre CAMHS

Key findings:

1. The majority (83%) viewed pre-pubertal bipolar disorder as "very rare", "rare" or "undiagnosable" and 53% had never seen a case in their professional career. In contrast, 57% saw adolescent bipolar disorder as "uncommon" and only 3% had never seen a case.

2. The results of the question "Estimate the number of pre-pubertal/adolescent cases of BD you have diagnosed in the last 12 months?" are presented in Figures 1 and 2, showing the differences between pre-pubertal children and adolescents.

3. Figure 3 shows that there was a divergence of views as to whether BD was appropriately diagnosed, under-diagnosed or over-diagnosed in Australia and New Zealand.

4. In contrast, there was a clear consensus that PBD was over-diagnosed in the USA, as illustrated in Figure 4.

5. Although a significant proportion were "unsure" or "neutral" as to whether "diagnostic upcoding" (giving a more serious diagnosis than warranted to access health care in the American private insurer dominated health system) was a causative factor, a majority (53%) felt it was and only 1.5% disagreed (Figure 5).

Appendix A5

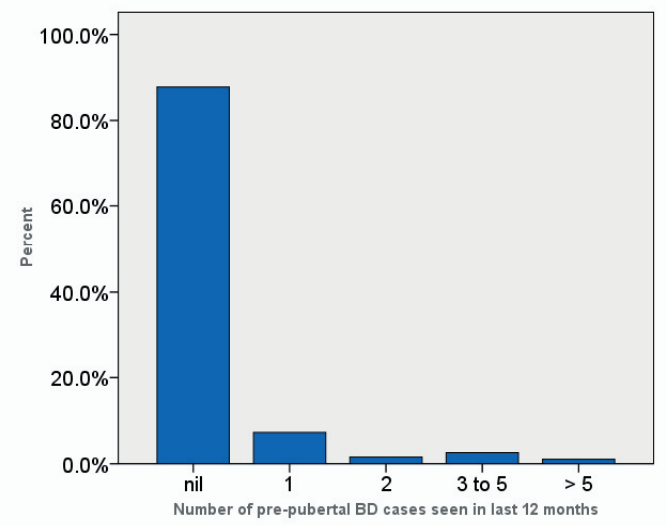


Figure 1. "Estimate the number of pre-pubertal cases of BD you have diagnosed in the last 12 months"

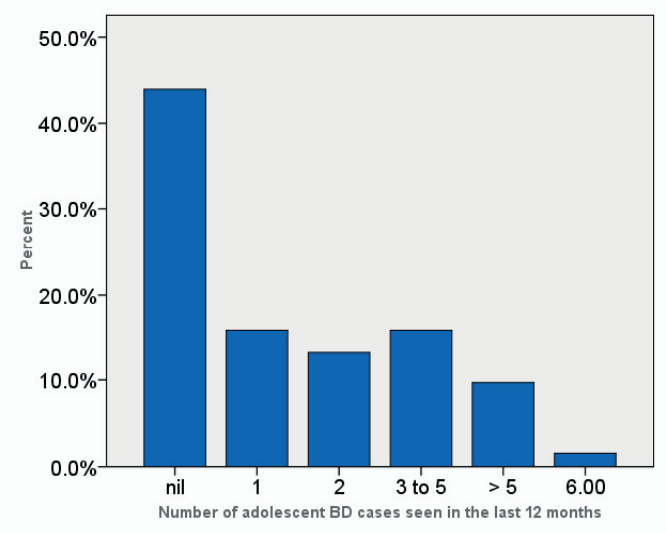


Figure 2. "Estimate the number of adolescent cases of BD you have diagnosed in the last 12 months"

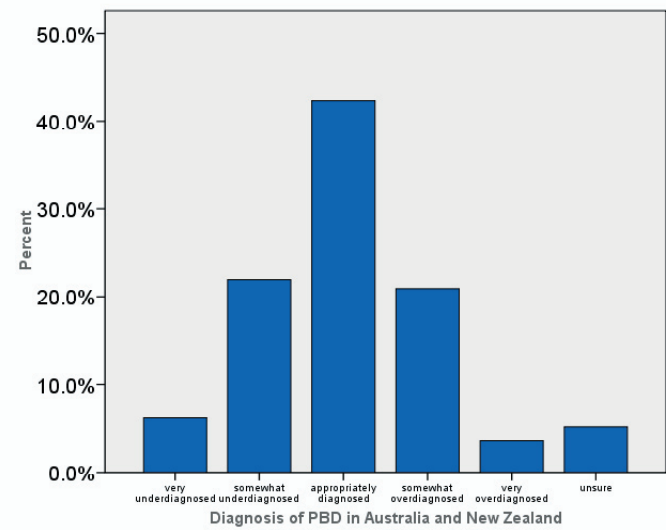


Figure 3. "In your opinion, PBD in Australia and New Zealand at present is overall…"

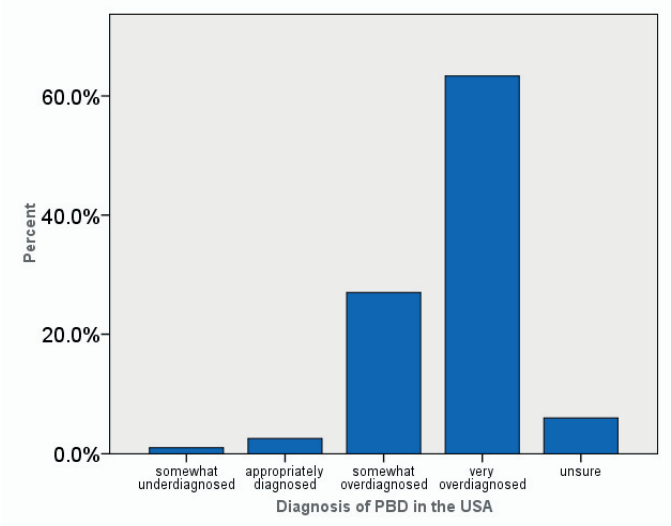


Figure 4. "In your opinion, PBD in the USA at present is overall…"

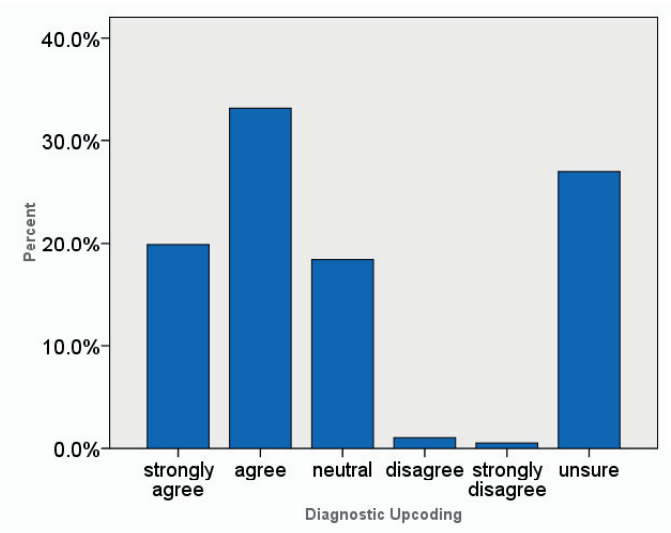


Figure 5. "Diagnosis up-coding to gain increased funding for therapy probably explains many of the cases of PBD in the USA"

Comments

75 of the 199 respondents gave comments. For reasons of length and lack of statistical validity these were not included in the paper published in 'Child and Adolescent Mental Health', however they add depth to the responses and several themes emerged. Examples are presented in the next page.

There were 11 comments generally favourable to increased diagnosis of paediatric BD. These tended to include some caveats about use of medication and noted issues of difficulty in diagnosis and comorbidity, e.g.:

"I am certain that PBD is under-diagnosed in Australia. However I also worry about the increasingly casual use of atypical antipsychotics in children and adolescents with apparently little concerns about metabolic side effects."

"…for many there has been inadequate time to clearly delineate all the features seen over years into adulthood, thus diagnosis is not always straightforward."

"I work in a specialist program for children and adolescents with or suspected/at risk of bipolar. Most cases are NOS [Not Otherwise Specified] and comorbidity is high."

There were eight references to the worth or otherwise of the survey, e.g.:

"It's silly asking us to speculate on opinions re. what's going on in the USA, as most of us don't have a feel for what's going on there..."

"Keep up the good work investigating and clarifying this disturbing phenomenon."

"It would be useful to survey paediatricians and to pass on results of this survey to RACP."

There were 18 comments on the theme of pendulum swing in psychiatry, e.g.:

"It is another fashion that will fade."

"I think PBD is the "new" epidemic as ADD has been/is …."

"I find the trend in the USA very worrying, anti-intellectual and counter-therapeutic."

"(I hope)…the crazy patterns of diagnosis in the USA don't happen in Australia."

Four comments that PBD followed over-diagnosis of BD in adults, e.g.:

"...diagnosis of BD in adults have risen dramatically over the past few years. This then places increased pressure for diagnosis of these children via 'genetic vulnerability'."

Ten comments about shift from the biopsychosocial to biomedical model, e.g.:

"Beware the medical model: the individual centered approach to psychiatric evaluation in children – their relationships are so crucial in their early development and in their day-to-day lives. I believe the diagnosis of BD in children is obscuring a range of parent-child relationship problems, parenting problems, attachment disruption, social and environmental factors."

"…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."

"There seems to have been a regressive paradigm shift in child psychiatry in the USA with a move back from a more holistic biopsychosocial approach to diagnosis and management to a reductionist biomedical model."

29 comments that alternative diagnoses in particular trauma- and attachment-related are overlooked, and that psychotherapies are often more appropriate e.g.:

"The definition of bipolar has become too flexible. Family/ contextual factors and a considered formulation may not be taken into account. There is a general problem in C&A psychiatry with prioritising diagnosis over formulation in my opinion."

"I have seen many cases diagnosed with BD which have not responded to medication, when in fact they have a cluster B personality disorder (adolescents) under 18 years. They have recovered once their PD symptoms and trauma were addressed in psychotherapy."

Seven comments referring to the health system in the USA, e.g.:

"The Americans rarely diagnose attachment disorders & disruptive behaviour disorders probably because they don't attract funding from HBOs. I believe many Bipolar II patients are misdiagnosed and are probably borderline personalities & when at APA I saw that many psychiatrists avoided Axis II diagnoses for HBO reasons, tending to opt for Axis I."

"The US managed care/insurance system influences what diagnosis is made & therefore what treatment can be provided. I have heard Boris Birmaher (a strong proponent of BD diagnosis) speak twice and am concerned about his diagnostic imprecision; at the Faculty conference in Darwin 2004 he stated 'we try not to make this (Borderline personality disorder) diagnosis' because when they want to refer them on for treatment no-one will take them. At ESCAP conference in Florence last month he stated 'It doesn't matter what you call it, these kids have mood swings.'"

Nine comments about the influence of the pharmaceutical industry, e.g.:

"Pharmaceutical companies appear to utilize massive resources to influence the diagnostic and therapeutic practice of all doctors including psychiatrists in the direction of "organic" disorders which require medications."

Two comments that normal range child and adolescent behaviours are being pathologised, e.g.:

"In adolescents, periods of intense boredom alternating with intense activity, prolonged sleep then staying awake for hours, talking for hours on end which I would regard as normal for the developmental stage have been interpreted... as symptoms of disorder especially Bipolar Disorder."

"Perhaps there is too much pathologising too soon these days."

Eight comments about deleterious effects of medication or the diagnosis on child's sense of self, e.g.:

"I find the practice of diagnosing BD in pre-pubertal children quite dangerous, particularly as some clinicians treat these children with potentially dangerous drugs (lithium especially)."

"We still know so little about the use of these drugs in children."

"families shift expectations/ perspectives in a way not helpful to the child's ego development/expectations of self."

"the diagnosis is more toxic in their lives and families than the extravagant medication they have been prescribed."

Peter Parry, Steve Allison, Gareth Furber
Flinders University, South Australia

Landmark Compensation Case over Zoloft in a Teenager

In a case believed to be the first of its kind in Australia, Nicola Mulcahy lodged a $95,000 claim for her own economic loss after she was forced to quit her job to take care of her daughter Hannah. Ms Mulcahy's daughter, aged 16, attempted suicide five days after being prescribed Zoloft. Several other attempts followed. She spent five weeks at the Royal Children's Hospital adolescent psychiatric unit. Ms Mulcahy said her daughter was later diagnosed with a genetic defect that predisposed her to having an adverse reaction to sertraline. In her statement of claim against the GP, Ms Mulcahy said the GP misrepresented and falsely promoted Zoloft as a safe, effective and approved drug for children. In her claim, Ms Mulcahy said she did not give informed consent because the serious side-effects associated with the drug were not explained.

It is reported she has reached a confidential legal settlement with the GP. She is now considering mounting a class action against the Therapeutic Goods Administration on the grounds that it failed to properly warn consumers and prescribers of the risks posed by anti-depressants. *Source: Julie-Anne Davies, The Australian, October 27, 2008*

BPAD Survey 2007 Qualitative Feedback

	Quote	Bias	Themes
1	The drug companies need new markets all the time for their profit and income and have a role in encouraging the debate about this diagnosis. Psychotropic medication is a major source of profit for the drug companies and all treating occurs in an economic/political context.	S	Ph Inf
2	As I am uncertain about American practice except by inference from my reading of journals and attendance at conferences, this only represents my opinion. I have discussed this issue with my colleagues here in the past and we all feel that we rarely see anything that looks like true BD in pre-pubertal children.	S	Alt Diag
3	Complex posttraumatic stress must be excluded or adequately treated before diagnosing PBD, and I think emotional dysregulation secondary to trauma/neglect/abuse/poor attachment is often misdiagnosed as mood cycling of PBD, which results in biological treatment and neglects the psychological.	S	Alt Diag MedMod
4	Pharmaceutical companies appear to utilize massive resources to influence the diagnostic and therapeutic practice of all doctors including psychiatrists in the direction of "organic" disorders which require medications.	S	Ph Inf MedMod Pen Swg
5	It is another fashion that will fade.	S	Pen Swg
6	I work and have done much of my training in children with complex trauma histories. These children often "achieve" multiple diagnoses. I wonder if the rise of BD in pre-adolescent children reflects sometimes an underestimate of the impact of trauma and its prevalence.	S	Alt Diag
7	Overdiagnosis is a major problem. There needs to be a major re-education of the public as well as some aspects of the profession regarding this.	S	Pen Swg
8	I am very disturbed and confused by paediatric (pre-adolescent) BD. Someone, either me or people in America are making big mistake over this diagnosis.	S	Alt Diag Pen Swg
9	Germ of truth contained in a currently fashionable diagnosis. As a profession we are still struggling to categorize the phenomena validly.	S	Pen Swg Diag Crit
10	Congratulations on doing this survey. Hopefully the crazy patterns of diagnosis in the USA don't happen in Australia.	S	Impt Svy Pen Swg
11	I find the trend in the USA very worrying, anti-intellectual and counter-therapeutic.	S	Pen Swg MedMod
12	In adolescents, periods of intense boredom alternating with intense activity, prolonged sleep then staying awake for hours, talking for hours on end which I would regard as normal for the developmental stage have been interpreted by other mental health practitioners (especially those with exclusively adult experiences) as symptoms of disorder especially Bipolar Disorder.	S	Alt Diag AdultBD
13	The Americans rarely diagnose attachment disorders & disruptive behaviour disorders probably because they don't attract funding from HBOs [Health Benefits Organisations – private health insurers]. I believe many Bipolar II patients are misdiagnosed and are probably borderline personalities & when at APA I saw that many psychiatrists avoided Axis II diagnoses for HBO reasons tending to opt for Axis I. This was also sponsored by drug companies who make fortunes from misdiagnosis (ADHD, PTSD) and psychiatrists can avoid giving years of psychotherapy or behaviour management which is probably required.	S	MedMod USAHS Pen Swg AdultBD Ph Inf
14	I think the sequelae of disturbed attachment and the sequelae of psychological trauma may account for the overdiagnosis of paediatric bipolar disorder. In Australia many of these children are incorrectly diagnosed as having ADHD.	S	Alt Diag
15	Keep up the good work investigating & clarifying this disturbing phenomenon.	S	Pen Swg Impt Svy
16	Perhaps there is too much pathologising too soon these days	S	MedMod Pen Swg

17	I think PBD is the "new" epidemic as ADD has been/is . I think it is driven by misguided medicalisation of developmental problems arising out of the pursuits of managed care and pharmaceutical interests.	S	Pen Swg MedMod USAHS Ph Inf
18	The US trend seems to be reflected here: certainly I have seen several post pubertal adolescents with a diagnosis of PBD who had other disorders/or family issues. It would be useful to survey paediatricians and to pass on results of this survey to RACP [Royal Australian College of Paediatricians].	S	Pen Swg Alt Diag Impt Svy
19	Beware of the medical model: the individual centred approach to psychiatric evaluation in children – their relationships are so crucial in their early development and in their day-to-day lives. I believe the diagnosis of BD in children is obscuring a range of parent-child relationship problems, parenting problems, attachment disruption, social and environmental factors.	S	MedMod Alt Diag
20	Many cases that I see have been diagnosed and medicated by paediatricians and some child psychiatrists who do not have a theoretical or practical understanding of the system surrounding a child and how any of the other diagnoses – especially trauma (DV, CSA) [domestic violence, child sexual abuse] impact pervasively on the child and family's functioning and how strategies other than just medication can help significantly.	S	Alt Diag MedMod
21	I am very concerned by the US trend and do believe it has impacted on clinical practice in Australia. Have found that diagnosis of BD in adults to have risen dramatically over the past few years. This then places increased pressure for diagnosis of these children via "genetic vulnerability". We still know so little about the use of these drugs in children. Concerns about our paediatric colleagues suggesting this diagnosis to parents prior to a mental health review by a psychiatrist.	S	Pen Swg MedTox AdultBD Gen
22	I suspect the unhealthy relationship between the drug companies and the profession has also had an unfortunate effect on this topic.	S	Ph Inf
23	I think many of the diagnoses of PBD are made by non-child psychiatrists – i.e., paediatricians and adult psychiatrists who often ignore developmental issues (such as affect dysregulation of adolescents) and systemic issues.	S	MedMod
24	In 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 BD or brief psychotic episodes. I see a number of women also with symptoms of BD who may more likely have borderline PD [Personality Disorder]. They get diagnosed as "rapid cyclers" rather than the problem being seen as affect dysregulation as a consequence of developmental trauma.	S	Alt Diag AdultBD
25	I think that a major problem is the unquestioning application of DSM-IV diagnostic criteria designed for the adult population to a disturbed and unstable paediatric population which may well meet the criteria threshold for bipolar disorder but whom most Australian clinicians would diagnose as suffering from other conditions.	S	Alt Diag AdultBD
26	Re question 16: unaware of therapy funding increases with diagnosis of PBD & what's the role of drug companies & medication subsidies in PBD in US?? Complex PTSD and emerging personality disorder often cause emotional dysregulation that may even respond effectively to treatment with mood stabilizers at times. The longitudinal history of such patients, in my clinical experience, reveals that the vast majority do not, in fact, have PBD. The lack of Australian epidemiological evidence, including treated prevalence of PBD, limit severely the reliability of comments we can make about questions 10 and 11. The Faculty should advise DHAC [**] to repeat the emotional health and well-being survey "The mental health of young people in Australia" (2006) by Sawyer, M to address this issue and advise re other diagnostic categories of national significance that should be surveyed by 2010.	S	Lack Kn Alt Diag Lim epid
27	What has been useful about the discussion of PBD has been the focus on affect dysregulation in this age group, not just fidgetiness and bad behaviour. My main concerns about the label "PBD" are that 1) a clear continuation to what has been known as the syndrome of adult BD has not been demonstrated. Thus families shift expectations/ perspectives in a way not helpful to the child's ego development/expectations of self, 2) it promotes a biological reductionist formulation and a focus on medication management, when many of these kids have clear contextual factors in terms of failure to develop internal affect regulation because of disruption in the provision of a containing/ regulating environment. Surely there is another way to highlight that these kids often have mood disorder family	S	MedMod Eff Self

	histories and are at risk for but don't have BD.		
28	Many cases also are borderline PD [Personality Disorder] with mood instability misdiagnosed as BD. Some European countries (e.g., Spain) are following USA. There has been a positive trial in the USA for Dialectical Behaviour Therapy for juvenile bipolar disorder. There are moves to alter the duration of episode DSM criteria to allow easier diagnoses.	S	Alt Diag Diag Crit Pen Swg
29	I agree with question 16 strongly. However I understand from US colleagues that the number and type of medication is also used as a marker of severity and hence funding. At one level the diagnosis would be considered to fit diagnostic criteria (or not). These vary. What seems critical is what understanding one makes of children who meet these criteria. PBD seems to imply an individualized, biological understanding.	S	USAHS Diag Crit MedMod
30	I have seen many cases diagnosed with BD which have not responded to medication, when in fact they have a cluster B personality disorder (adolescents) under 18 years. They have recovered once their PD symptoms and trauma were addressed in psychotherapy. Very timely survey – we are going the way our American colleagues are going both in overdiagnosis of ADD, ADHD and BD. DSM diagnostic symptoms are to blame for this.	S	Alt Diag Pen Swg Diag Crit Impt Svy
31	The definition of bipolar has become too flexible. Family/ contextual factors and a considered formulation may not be taken into account. There is a general problem in C&A psychiatry with prioritising diagnosis over formulation in my opinion.	S	MedMod Diag Crit
32	Currently bipolar II disorder appears to be overdiagnosed in adults	S	Pen Swg AdultBD
33	Attendance at Oxford conference 2007 – statement by Prof Guy Goodwin highlights also the fact of USA using broad bipolar phenotype whereas my choice and UK choice is for strict BPID phenotype.	S	Diag Crit
34	I am strongly in favour of treating symptoms as they arise however to label children so young is frequently inappropriate.	S	Alt Diag
35	I am increasingly worried by children/ adolescents arriving with American PBD diagnoses. The diagnosis is more toxic in their lives and families than the extravagant medication they have been prescribed. I see this phenomenon as similar to the American overdiagnosis of schizophrenia in the 1950's → 1960's.	S	Eff Self Med Tox Pen Swg
36	In my own practice I have noticed inpatients who had symptoms of affective instability, sleep disturbances, externalising behaviours and some with auditory or visual hallucinations to stabilize with a period of time spent in the inpatient setting without the use of mood stabilizers or antidepressants. Sometimes we prescribe an atypical antipsychotic in low dose as a general non-specific intervention as a sedative or anxiolytic. I attribute these changes to a stable ward, predictable routines and clear boundaries. Many of these children with ? Bipolar diagnoses come from very prejudicial background with abuse as a theme of their presentation.	S	Alt Diag
37	There are certain services in Sydney that are virtually guaranteed to diagnose BD – akin to the notion of ADHD clinics only recognizing ADHD to explain all ills. I think BD is overdiagnosed (and too early) in North America. I find the practice of diagnosing BD in pre-pubertal children quite dangerous, particularly as some clinicians treat these children with potentially dangerous drugs (lithium especially).	S	MedMod Few Enth Med Tox
38	There is so much fluidity in symptoms in young children, we should be very cautious diagnosing BD in very young children. The supposed "overlap" between ADHD and BD, in particular reflects sloppy clinical skills in my view.	S	Alt Diag
39	Drug company propaganda and failure to treat ODD/CD – lack of services has medicalized many disruptive disorders.	S	Ph Inf MedMod Alt Diag USAHS
40	The wrongly diagnosed I see are by people, mostly medicos who have ?skills in differential diagnosis and in the management of the disruptive disorders, that they like the medication (& adjustment thereof) as their service. Some doctors are obsessed by bipolar. My work referred to by John Bowlby is in "Loss".	S	MedMod

41	Not only funding for therapy but also research. Many clinicians started off with some insight into using diagnosis as one of convenience but with a new generation of clinicians brought up with this thinking, the insight is being lost.	S	Ph Inf MedMod
42	The US managed care/insurance system influences what diagnosis is made & therefore what treatment can be provided. I have heard Boris Birmaher (a strong proponent of BD diagnosis) speak twice and am concerned about his diagnostic imprecision; at the Faculty conference in Darwin 2004 he stated "we try not to make this (Borderline personality disorder) diagnosis" because when they want to refer them on for treatment no-one will take them. At ESCAP conference in Florence last month he stated "It doesn't matter what you call it, these kids have mood swings." Also his inpatient unit used DBT [Dialectical Behaviour Therapy] (demonstrated effectiveness for borderline personality disorder/affect dysregulation); and he works with the families/parents too. He essentially sees kids with affect dysregulation from a variety causes, uses a combination of treatments, yet states that they have bipolar disorder and respond to medications.	S	USAHS MedMod Alt Diag
43	This is a serious issue at day to day practice. it is much easier to give away medication rather than time consuming, multidisciplinary approach to children's behaviour or even mental illness. Even if there are many cases of bipolar juvenile form, psychosocial and environmental approach might be a better and might have a long lasting effect. It breaks my heart when I see so called juvenile bipolar who turned out to have learning difficulties, ADHD and family issues (these issues not totally ignored and not addressed because it is time consuming and dealing with difficult parents!), the most damaged person in the process is the child. I have come across boys losing self esteem as they [see themselves] as "bipolar" and excuse their bad behaviour as "bipolar". Poor parenting, political power problem, easy solution for kid's problem blaming kid, drug company and lazy psychiatrists, we are all responsible for this ugly trend. Pure biological approach in children's behavioural problems in child psychiatry in the USA due to political and financial conflict has a serious ramification. Most of all, children have no say in taking serious medication for so called "behavioural problem" This year, at Pittsburgh conference, international bipolar conference, the diagnosis criteria for juvenile bipolar is " irritability".	S	MedMod Alt Diag Eff Self USAHS Ph Inf Diag Crit
44	I have received a few inquiries from concerned parents about affective instability in children and adolescents. They ask “Could this be bipolar disorder?” In all these instances the affective instability has been more directly related to disrupted lives and trauma. As yet, none that I have followed have gone on to develop severe and sustained mood swings consistent with an emerging bipolar disorder. This could happen but it seems to be unusual compared with the more common causes of emotional instability.	S	Alt Diag
45	see very good paper by Gabrielle Carlson and S Meyer in Development and Psychopathology 18 (2006), 939-969. My experience and review of the literature is exactly the same. I think the main reason in the US is advertorial by the Big Pharma.	S	MedMod Ph Inf
46	I believe it is abusive to very young children, especially pre-school children, as is happening in the USA, to be given the diagnosis of BD. 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.	S	Eff Self Med Tox MedMod
47	There seems to have been a regressive paradigm shift in Child Psychiatry in the USA with a move back from a more holistic biopsychosocial approach to diagnosis and management to a reductionist biomedical model. The economics of the American health system and the very high input of pharmaceutical industry into CME [Continuing Medical Education] in the USA may explain this, and then the whole idea gets a momentum of its own with researchers shifting criteria to give the disorder legitimacy. I sincerely hope we avoid such a path in Australia and New Zealand.	S	MedMod USAHS Ph Inf Diag Crit Pen Swg
48	Manic episodes relating to substance use might also explain some additional diagnoses in US populations.	S ?N	Sub Use
49	I believe majority of my colleagues are appropriately diagnosing in small numbers. However, single practitioners diagnosing at frequent intervals will skew this result.	S ?N	Few Enth
50	There is confusion around caused by asking what disorder before asking whether there is disorder and how severe is it. Functional impairment with a clear episodic deterioration with volatility is a better	N	Alt Diag Diag Crit

	guide to juvenile illness than persistence of manic symptoms. Driven and desperate is much more common in the mixed juvenile picture than elated and euphoric.		
51	In Australia it seems PBD diagnosis is much more common with some practitioners & this may also be case in USA. My neutral coding in Q 13 14 16 reflects that "many" might be confounded by individual factors and that in fact all factors probably contribute to overall differential diagnostic rates, compounded by the difficulties in making accurate syndrome diagnoses in children with any predictive value.	N	Diag Crit Alt Diag Few Enth
52	I do not feel experienced enough to give opinion on US diagnosis/prevalence rates. Consider my opinions informed guesses.	N	Lack Kn
53	I am glad you made the distinction between "opinions" and prevalence data. I am a bit of an outlier. I am an American who works in the US and New Zealand.	N	
54	Depends on definitions of bipolar I and II & "not otherwise specified".	N	Diag Crit
55	I only have a small practice and limited experience in this area.	N	Lack Kn
56	I am now 77 and have not treated C& A in-patient for over 7 years. Currently I see adolescents and adults with pervasive developmental disorders, a few of whom have BPD.	N	
57	As a CL psychiatrist I see few cases of PBD so my data may be an underestimate of inpatient or even community psychiatrists.	N	
58	I have been somewhat confused and concerned about the number of cases of PBD I must have been missing. However other treatment approaches often adequately deal with the presenting problems in my practice.	N	Alt Diag
59	I don't claim to have all the answers – just 20+ years clinical experience	N	
60	Need to actually decide if PBD is same diagnostic criteria as for adult BD – e.g., mood elevation/ irritability 4/7 and not in response to external event.	N	Diag Crit
61	I practiced child psychiatry in the US for 15 years before I came to Australia so I am reasonably well acquainted with both systems.	N	
62	I don't think I can comment on what people are diagnosing in the USA – I don't know.	N	Lack Kn
63	Its silly asking us to speculate on opinions re. what's going on in the USA, as most of us don't have a feel for what's going on there. Thus our guesses are going to be very uninformed.	N	Lack Kn UnimSvy
64	I doubt the usefulness of this survey.	N	UnimSvy
65	There are some cases (e.g., severe major depression) in a young adolescent where the presence of type 1 bipolar disorder in a first degree relative has led me to diagnose bipolar disorder in the absence of clear manic symptoms.	A	Gen
66	Bipolar does occur in pre-pubertal children but I believe is still uncommon in that group. In post-puberty adolescents bipolar disorder is common but for many there has been inadequate time to clearly delineate all the features seen over years into adulthood, thus diagnosis is not always straightforward.	A	Comorb
67	As a psychiatrist doing inpatient work I see significant numbers of bipolar adolescents. Pre-pubertal cases are seen but rarely. This question does however arise in differential diagnosis quite frequently. Would also wonder what part stimulant abuse and other drug use plays in overdiagnosis, especially in the USA. I have certainly become much more aware of paediatric bipolar disorder over the last 5-10 years. Whilst I saw cases in the early years of my practice these were quite rare.	A	MedTox Sub Use Comorb
68	Paediatric BD is very topical therefore survey seems timely. In general it is overdiagnosed by paediatricians and underdiagnosed by GPs and adult psychiatrists. I have seen a clear trend between parental BD and BD symptoms in teenage offspring.	A	Gen Impt Svy

69	The prevalence answers depend very much on case definition: I work in a specialist program for children and adolescents with or suspected/at risk of bipolar. Most cases are NOS [Not Otherwise Specified] and comorbidity is high.	A	Diag Crit Comorb
70	It is very difficult to know if first presentation depression/anxiety is BD and this causes high level of anxiety for clinicians who are aware of potential for it being an early sign of BD.	A	Diag Crit Comorb
71	I am certain that PBD is underdiagnosed in Australia. However I also worry about the increasingly casual use of atypical antipsychotics in children and adolescents with apparently little concerns about metabolic side effects.	A	Med Tox
72	Thankyou – an important questionnaire. There is no doubt that some of these young people, especially adolescents have been missed and have suffered recurrent episodes of depression. These young people probably pose a greater diagnostic challenge then when one is assisted by the revelation of a manic episode. It was our practice to follow them on for years, into young adulthood and into their 30's. Don't forget also that one can have comorbidity – major depression with some of the syndromes cited in question 15.	A	Comorb Impt Svy
73	"*PBD in Australia/New Zealand is somewhat underdiagnosed*" in primary health care/ GP's understandably. "*PBD in Australia/New Zealand is somewhat underdiagnosed*" in specialist psychiatric services in the adolescent years; often in my own clinical experience, many had been assigned a diagnosis of schizophrenia or personality disorder. *"PBD in the USA at present is somewhat overdiagnosed"* – this would seem to be the case. I would want a rigorous family history, assess the family tree for affective disorder symptoms, creativity, eccentricity etc etc. *"A significant proportion of other diagnoses (e.g., ADHD, anxiety……"* – this is too sweeping a general statement. Each child/adolescent/family should have a sensitive and extensive assessment and review if necessary with another consultation to arrive at the most accurate diagnosis.	A	
74	At present I'm working with families who have experienced extreme trauma and not seeing in general "child and family" section of population. When working in public system encountered hostility, mostly from ? and other psychiatrists when diagnosing bipolar in young people (under 18).	A	
75	I have read the USA arguments. I have seen 14 cases of PBD under puberty and possibly I have underdiagnosed it (i.e., 14 should be 28) but that still makes it rare (very)!	A	

Minor typographical errors corrected.
Acronyms such as PBD and BD have been standardised and other acronyms explained in square brackets.

Key to themes:

Adult BD = Influence of expanding diagnosis of adult BD.

Alt Diag = Alternative Diagnoses more likely, includes biopsychosocial systemic and developmental perspective.

Comorb = Comorbidity

Diag Crit = Diagnostic Criteria issues

Eff Self = Effect upon Self Development for child of a PBD label.

Few Enth = Few Enthusiasts = observation that a minority of practitioners diagnose majority of cases.

Gen = Genetic aspects.

Impt Svy = Important Survey = comments that survey is important.

Lack Kn = Lack of Knowledge of USA Health System.

Lim Epid = Limited Epidemiology = observation that there is limited good epidemiological data re PBD.

MedMod = Medical Model = observations and opinions re reductionist biomedical model, often contrasted with biopsychosocial systemic and developmental perspective.

Med Tox = Medication Toxicity = concerns regarding toxicity and side-effects of medication for children with PBD diagnosis or other medication like stimulants/antidepressants inducing mood instability.

Pen Swg = Pendulum Swing = observation and opinions about PBD being part of a "fashion" or pendulum swing in diagnostic practice.

Ph Inf = Pharmaceutical company influence.

Sub Use = Substance Use = Substance use as trigger for agitated or hypomanic behaviour that may lead to a BD diagnosis.

UnimSvy = Unimportant Survey = Opinion that the survey was unnecessary.

USAHS = USA health system.

Tuesday, May 19, 2009

5. **Current and Future of Other Brain Stimulating Techniques**
   Alexander Bystritsky, M.D.

Discussant: Laura B. Dunn, M.D.

SYMPOSIUM 31 2:00 P.M.-5:00 P.M.

Room 304, Esplanade Level, Moscone Center

PEDIATRIC BIPOLAR DISORDER: A CRITICAL LOOK AT AN AMERICAN PHENOMENON.

Chp.: Peter I. Parry, M.B.B.S.

1. **Australian and New Zealand's Child & Adolescent Psychiatrists' Views on Bipolar Disorder Prevalence and on Rates of Pediatric Bipolar Disorder in the USA.**
   Peter I. Parry, M.B.B.S.

2. **Changing the Treatment Culture in a Residential Agency for Youth: Broadening the Role of Psychiatry**
   Edmund C. Levin , M.D.

3. **Pediatric Bipolar Disorder: A Dispassionate Review of the Literature**
   Glen R. Elliott, M.D.

4. **Bioethics and "Pediatric Bipolar Disorder"**
   Mary G. Burke, M.D.

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SYMPOSIUM 31

PEDIATRIC BIPOLAR DISORDER: A CRITICAL LOOK AT AN AMERICAN PHENOMENON.

EDUCATIONAL OBJECTIVES:

At the conclusion of this session participants will be able to; 1) understand the controversies surrounding the PBD diagnosis; 2) have a clear clinical understanding of the differential diagnosis of severe emotion dysregulation in children; 3) understand the contextual factors that have contributed to the increase in the PBD diagnosis and the associated use of medications; 4) consider the pitfalls of using adult disease models in children; and 5) be able to use the methods of bioethics to make clinical decisions in children previously diagnosed with PBD.

NO 31A

AUSTRALIAN & NEW ZEALAND CHILD & ADOLESCENT PSYCHIATRISTS' VIEWS ON BIPOLAR DISORDER PREVALENCE AND ON RATES OF PEDIATRIC BIPOLAR DISORDER IN THE USA

Peter I Parry, M.B.B.S., Marion CAMHS, PO Box 248, Oaklands Park Adelaide 5050 Australia

SUMMARY:

There has been a surge in diagnosis of paediatric bipolar disorder (PBD) in the USA over the past decade, in particular cases of pre-pubertal PBD. This has yet to be generally replicated in Australia or New Zealand.

The aim of this study was to survey the views of members of the Faculty of Child and Adolescent Psychiatry (FCAP) of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) with regards to PBD as to perceived prevalence, diagnostic practice and views as to why the diagnosis may have increased so dramatically in the USA.

A 16 question plus open comments survey was sent to the 328 members of the FCAP of the RANZCP currently based in Australia and NZ.

Results suggest the majority of respondents hold to traditional views that bipolar disorder is very rare in children and uncommon in adolescence. The survey had a 60% (n=199) response rate and most (53%) reported never having diagnosed bipolar disorder in the pre-pubertal age group and a further 29% estimated only ever seeing "1 or 2" cases. Most (83%) rated pre-pubertal cases as "very rare", "rare" or "not diagnosable". In contrast over 96% had diagnosed adolescent cases of bipolar disorder. Opinion varied as to whether PBD was over-diagnosed (24.5%), appropriately diagnosed (42%), or under-diagnosed (28%) in Australia and New Zealand, 5% were unsure. In contrast there was a consensus of views that PBD was over-diagnosed in the USA (90%), whilst less felt it appropriately diagnosed (3%), or under-diagnosed (1%) and 6% were unsure.

Taken in conjuction with results of a similar survey of German child & adolescent psychiatrists and the British National Institute for Health and Clinical Excellence (NICE) guidelines (2006) on Bipolar Disorder, such views support assertions that PBD remains a controversial diagnosis with limited penetration outside the USA.

NO 31B

CHANGING THE TREATMENT CULTURE IN A RESIDENTIAL AGENCY FOR YOUTH: BROADENING THE ROLE OF PSYCHIATRY

Edmund C Levin , M.D., 2424 Dwight Way, #2, Berkeley CA 94704

SUMMARY:

The task of psychiatrists serving youth in residential programs has largely shifted to diagnosis and prescribing medications. The author was able to define his role differently and was able to explore the consequences of emphasizing the role of trauma in determining the thinking, feeling and behavior of children who presented with extreme irritability and marked shifts in moods. Because such rageful children have increasingly been seen as biologically disordered, many have been given the diagnosis of pediatric bipolar disorder and thus are frequently admitted to residential programs on high doses of multiple medications which are drawn from several different classes of psycho-pharmaceuticals. When tapering trials of these medications were first attempted, it was quickly determined that changes in institutional culture, diagnostic understanding and treatment were needed to allow for successful reductions of medications and for effective psychodynamic therapy. The institutional culture was modified as new approaches to staff development, enhanced functioning of the treatment team, new ways of understanding patients and new treatment interventions were developed to facilitate working with children on less or no medication. Ultimately, when team consensus could be obtained, sequential tapering trials of medications were performed. Relevant literature is reviewed and clinical material is used to illustrate the process and consequences of change in the institutional treatment culture. Results: The number of children receiving medication, the amount and number of medications used, and the number of aggressive incident reports fell dramatically over a 2-year period. Manifestations of past trauma, rather than biochemical disorders, became the dominant focus of an analytically informed treatment. Conclusion: Treatments based more on psychodynamic and developmental considerations and less on an exclusive neurobiologic conceptualization can be efficacious.

SYMPOSIA

NO 31C

PEDIATRIC BIPOLAR DISORDER: A DISPASSIONATE REVIEW OF THE LITERATURE

Glen R Elliott, M.D., 650 Clark Way, Palo Alto, CA 94304

SUMMARY:
Over the past 20 years, pediatric bipolar disorder has become a hotly contested topic, especially in the U.S., with published research and clinical opinion offering a potpourri of results about its prevalence, meaning, and appropriate treatment. More conservative approaches have focused on seeking to identify children who have a high likelihood of developing typical signs and symptoms of bipolar disorder as adults. Others have attempted to explore possible overlaps of bipolar disorder with high-prevalence childhood disorders, especially Attention-Deficit/Hyperactivity Disorder (ADHD). Still others have suggested that pediatric bipolar disorder may be the etiologic factor in a wide array of behavioral disturbances in children, including mood lability, impulse dyscontrol, and temperamental fragility. This presentation will review that literature, emphasizing how the different groups interested in this phenomenon have defined their terms and highlighting the relative advantages and limitations of the differing approaches to labeling children with this disorder. Where possible, the review will include published findings about treatment implications and known outcomes.

NO 31D

BIOETHICS AND PEDIATRIC BIPOLAR DISORDER

Mary G Burke, M.D., 1801 Vicente Street, San Francisco, CA 94116

SUMMARY:
"Pediatric Bipolar Disorder" (PBD) has engendered controversy since it was first described. This presentation summarizes the major ethical problems and dilemmas associated with PBD; it recommends the methods of bioethics to clarify both research and clinical questions.

Using a bioethical framework, the presentation reviews the following aspects of PBD: 1) Conflicts of interest and close ties between PBD researchers and the pharmaceutical industry. 2) The narrow focus of academic research on children with severe mood dysregulation, vs. the clinical realities of community populations. 3) Clinical problem-solving. Jonsen's clinical bioethics grid, and Murray's concept of "Mutualism" will be explained. These principles will be applied to clinically derived examples posing specific ethical dilemmas in the treatment of severely disturbed children previously diagnosed with PBD. By the end of the presentation, attendees will be able to use a bioethics framework to make decisions about the treatment of children with severe emotion dysregulation, and more critically assess research publications.

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SYMPOSIUM 32
WORKING WITH LAWYERS

EDUCATIONAL OBJECTIVES:
Because of it's practical sharing of experiences along with analytic, erudite and esoteric ideas, at the conclusion of this session, the participant should have a fairly solid understanding of "the good, the bad, the ugly, the tricky, and the glorious" that can occur when Working With Lawyers.

NO 32A

VALUES OF MEDICINE AND THE LAW

Roger Peele, M.D., P O Box 1040, Rockville, MD 20849-1040

SUMMARY:
The values of the judiciary have a major impact on the values of medicine. Both the judiciary and medicine value a careful, respectful focus on the individual, but their approach to this focus clash. Whereas the judiciary assumes an inherent conflict between the parties in pursuing justice, medicine assumes no inherent conflict in pursuing health. The judiciary pursues its factual determinations formally, adversarially, and with highly rationally rules of evidence, medicine pursues its factual determinations informally, cooperatively, and empirical rules of science. The judiciary's fact determinations are made by laypersons, medicine's fact determinations are made by experts. Judicial decisions as to facts represent the endpoint, are fixed and final. Medicine's decisions as to facts are early, flexible and subject to change. Judiciary's focus in review is on process and scholastically based, medicine's focus in review is on results and empirical based. Judiciary's concern about error is expressed in the thought that better ten persons be found innocent than one person be found guilty. Medicine concern about error is expressed in the thought that better ten people be hospitalized unnecessarily than one die. The judiciary's adopted theories become permanent, medicine's adopted theories are tentative and subject to empirical tests. Judiciary has to assume a free will, to preserve a sense of culpability. Medicine has to assume deterministic models to achieve therapeutic predictability.

NO 32B

Cough disorder: an allegory on DSM-IV

Peter I Parry

The DSM-IV is more a reliable descriptive nomenclature than a valid classification of diseases

The *Diagnostic and statistical manual of mental disorders*, third edition (DSM-III), published by the American Psychiatric Association in 1980, sought to define psychiatric syndromes in a way that increased the reliability of psychiatric terminology and diagnoses between practitioners and nations. The DSM-III's introduction cautioned that, with regard to aetiology, it was a "generally atheoretical" document. The subsequent edition, the DSM-IV, published in 1994, went further, and cautioned specifically against diagnoses being applied in a "cookbook" fashion. Despite these warnings, conversion of the description of psychiatric disorders to discrete disease entities has not only occurred but, I believe, has also become problematic. Here, I present an allegory of a boy with "cough disorder" to illustrate.

It was time for the annual post-prandial Christmas dinner nap. A niece was coughing on inhaled lemonade. Dreams are often allegorical; it had been a busy year, and I started to dream.

"Cough disorder" — a dream

A mother came into my consulting room with her son. "He's got cough disorder", she declared. She'd read the symptoms on the internet: "a short, repetitive noise coming from the throat associated with the expulsion of air from the lungs".

This was, indeed, true. The website had quoted the DSM-IV. That is, the fourth edition of the *Diagnostic and statistical manual of human noises* published by the American Phoniatric Association.

"He's clearly got cough disorder, and he needs Suppressalin cough suppressant", the lad's mother said. Suppressalin had been advertised via a link on the "Help for Parents of Kids with Cough Disorder" website. The young chap himself broke into a succession of hacking coughs as if to emphasise the problem, at which point his mother widened her eyes and slowly and firmly nodded, to emphasise the obviousness of the diagnosis. One that, presumably, was now even more clearly in need of the advertised pharmacotherapy.

I sighed. That is, I "exhaled in concert with slight laryngeal constriction, following a deep diaphragmatic inhalation", making a "soft, rather low-pitched noise", and this occurred "in a situation of frustration, tension, tiredness or boredom". (I noticed my noise, recognised I was in a situation of frustration, and recalled research showing I'd just stimulated my vagus nerve to maintain autonomic nervous system equilibrium.)

I coughed, but it was the "ah hem" subtype; the "short, sharp, double noise emanating mainly from the larynx without significant pulmonary air expulsion". This is not normally considered a pathological cough, although I noted the lad's mother raised an eyebrow. I knew my "ah hem" cough was the prelude to my well worn (and weary) noise-educative spiel to parents of coughing kids.

"Well yes, he does cough; I totally agree with you there", I said, to get mum on side, and noticed a slight easing of her wary defensiveness. "But you see 'cough disorder' doesn't tell us very much. It is not really a diagnosis but a description of behaviour." She was starting to resume the wary defensive posture; the boy uttered a quick succession of coughs. I decided to look grave and said how concerning his coughing was, and that it was very important we thoroughly investigated it. She said the parents' help website had indicated that Suppressalin was exactly what was needed, but I noticed she was now less certain, and I made a "hmmm" sound in a particular way, to indicate understanding and empathy, but also that I knew more. I was, after all, the doctor. I sensed she seemed willing to listen to the spiel.

"Cough disorder is simply a description, a starting point", I said. "We have to find out why your young man here is coughing. Cough disorder can have many causes, and, for some children, several causes can combine." I went on to describe inhaled objects, drinks down the wrong way, asthma, croup, bronchitis, pneumonia, pharyngitis (the tickly throat cough), postnasal discharge, and rarer, more serious causes, such as throat and lung cancer, pneumothorax, bronchiectasis, silicosis and congestive cardiac failure. It could be a reaction to dust or cold dry air; there is always an environmental context. And, it could even be something as mild as a frequent habitual "ah hem" cough to try to gain attention.

I had the lad's mother's attention now, and the lad himself had also stopped coughing and was listening. I said that his cough may not need Suppressalin (although I acknowledged that, for some kids, Suppressalin is very beneficial, and they may need it for many years). We went on to look collaboratively for what was causing the cough. Even dad came to the next consultation. I also had an informative telephone discussion with the child's teacher, who told me how the boy generally stopped coughing by morning recess.

The problem with the DSM

The astute reader may by now have guessed that my "dream" is an allegory about attention deficit hyperactivity disorder (ADHD), and that, by corollary, the "DSM of human noises" is the *Diagnostic and statistical manual of mental disorders* published by the American Psychiatric Association, currently in its fourth edition.[1] The DSM is sometimes referred to as psychiatry's bible. However, like the Bible, it should be mainly read as descriptive, not literal, truth.

The problem dates primarily from 1980 and the publication of the DSM-III. At the time, psychiatric terminology suffered from a different problem — psychiatrists using the same labels for different conditions; in particular, schizophrenia, which was overdiagnosed in the United States compared with Europe (and Australasia).[2] The DSM-III devised "operationalised criteria" — lists of symptoms to define descriptive "disorders", so that everyone would at least know what behaviour was being described when a term like "schizophrenia" was used. Reliability is a necessary step on the road to validity. The DSM-III brought about a more reliable nomenclature and a more robust definition of syndromes, a vital prerequisite for psychiatric nosology (the branch of medical science dealing with the classification of diseases) to advance. However, the DSM-III was not meant to be read as a valid classification of diseases, even though it aspired towards that goal. Diagnoses in other areas of medicine also vary in

levels of understanding of aetiology (eg, migraine is still a syndromal diagnosis, and hypertension is a diagnosis based on deviance from normative dimensions); however, the level of scientific knowledge is more advanced in many other areas, and many disease states are well understood. Psychiatry is not so far advanced.

A further complicating factor in psychiatry is the, as yet, unresolved mind–brain problem,[3] and that for such a social species as *Homo sapiens*, the psychosocial and intersubjective domains, including narrative and meaning, are not easily accessed by symptom checklists. The DSM-III and DSM-IV attempt to address this with their multi-axial approach to a range of factors, such as personality, concomitant medical disorders, psychosocial stressors and level of functional impairment, as well as the "V-code" diagnoses — codes used to indicate problems that aren't clinical disorders — such as "parent–child relational problem".

Further complicating nosology is the issue of multicausality and equifinality — syndromal end states may comprise a clustering of individuals with quite different aetiologies for similar presenting symptoms. This is implied in the DSM introductions, with the DSM-III purporting to take a "generally atheoretical stance" with respect to aetiology, and the advice in the DSM-IV that it is "not to be used in a cookbook fashion". Despite these warnings, all too often, collections of symptoms classified as disorders tend, in practice, to be thought of as disease entities in their own right. This is less problematic for severe psychotic disorders such as schizophrenia and manic-depressive psychosis (now called bipolar-I disorder in the DSM-IV), which likely represent underlying brain disease. However, I do think that it is problematic with what used to be called "neuroses", and symptoms that overlap with temperament, personality and responses to stress and trauma, where the interactions of brain, mind, body, relationships and environment are multidirectional.

So the problem is not so much with the DSM itself, but with the way it is often used pre-emptively.

My allegory on ADHD could apply to "conduct disorder", "oppositional defiant disorder", "school refusal", "autism spectrum disorder" or, particularly in the US, the controversial "paediatric bipolar disorder"[4] which, although it is not defined in DSM-IV, can be argued reflects an overly reductionist "neo-Kraepelinian" approach[5] that common use of the DSM tends to foster. A similar problem occurs with anxiety, depression and adult "bipolar spectrum disorders". The problem of seeing all depressive states as homogeneous, differing only in severity, has been raised previously.[6]

In his 2005 presidential address to the Royal Australian and New Zealand College of Psychiatrists (RANZCP), Boyce referred to a "dumbing down" of psychiatry by using the DSM for simplistic "cookbook" diagnoses. He also referred to the pharmaceutical industry's pervasive influence in medical research and medical education.[7,8] In psychiatry, this influence often supports a reductionist biomedical model of human emotional and behavioural problems, rather than the systemic biopsychosocial model upheld by the RANZCP. A simplistic cookbook approach to the DSM would, indeed, seem to be in industry's interests, as behavioural symptom clusters get reified to disease states, and marketing to both the medical profession and the public can support a "pill for every ill" approach.[9] Such marketing finds fertile ground — in a busy world, the siren call of such simplicity in diagnosis and treatment is appealing to both the public and the medical profession.

Such misapplication of psychiatric nosology was predicted two decades ago as the rise of "biologism",[10] and eloquently expressed by Lipowski in his 1988 presidential address to the Canadian Psychiatric Association as the rise of "mindless psychiatry".[11] (Lipowski also noted the perils of the other extreme — "brainless psychiatry" — in which all psychopathology is seen in only psychosocial terms, something this essay is not advocating.) DSM-associated biomedical reductionism has been noted by many American psychiatrists.[12]

In contrast, an alternative approach to psychiatric nosology proposes the "four perspectives of psychiatry" ("disease, dimension, behaviour, life story"),[3] which is a more radical multi-axial approach than the DSM axes and seeks to balance the neo-Kraepelinian disease approach with the "neo-Meyerian" focus on biopsychosocial case formulation.[13] It was described in a course at the recent American Psychiatric Association annual meeting titled "Going from the bio-bio-bio model forward to bio-psycho-social reasoning".[14]

Where disorders most likely fit the disease model, as with the psychoses, there are promising proposals to refashion the upcoming fifth incarnation of the DSM — the DSM-V — to move beyond the descriptive approach and attempt to base psychiatric classification on underlying causes.[15] Further changes proposed include greater emphasis on dimensional measures (eg, to look at subsyndromal risk factors for depression and possible prodromal psychotic symptoms, like suspiciousness, that may aid early detection), rather than categorical measures (such as currently, when meeting sufficient criteria indicates disorder, and below that implies no disorder) to better reflect clinical reality. On the other hand, the head of the former DSM-IV taskforce has expressed strong concern that such moves are premature, would "flood the world with ... false-positive patients" who "would pay a high price" in stigma and by being overmedicated and, with respect to problems like excessive Internet use, that expansion of criteria in the DSM-V would further "inappropriately medicalise behavioural problems".[16]

Despite, or even because of, this problematic nosology, psychiatry remains a complex but compelling and rewarding profession that requires time, and experience, patience and wisdom acquired through clinical and life experience in helping those who come for help. There are no short cuts, DSM or no DSM.

Return to our allegorical dream of cough disorder

The dream ended happily. The lad and his parents came to understand that cough disorder was not a diagnosis but a description, and that his real problem — mild asthma — required a different medication, and then no medication at all when his parents stopped smoking in his presence. We had tried Suppressalin at one point, but it gave only short-term relief.

The parents and I even had a more philosophical discussion about how the third edition of the DSM of human noises focused on defining human noises descriptively, at a time when some doctors talked about "cough" when they really meant "sneeze", "burp" or "hiccup", and how that was a good development back in 1980. But we also discussed how, as an atheoretical descriptive system, it generally gives no information about underlying causes, and how important the search for real causes is; this is something the family now appreciates.

During my last session with this family, there were several repetitions of "ah yes" and "hmmm" (shorter, higher pitched

subtype, usually indicative of agreement) — all, in my opinion, completely non-pathological noises, although I understand some do think them overused and claim to have medications for them.

. . . I awoke. My niece was playing happily with her Christmas presents. The cause of her coughing — inhaled lemonade — had cleared.

Competing interests

None identified.

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(Received 16 Jun 2009, accepted 24 Sep 2009) ❑

Appendix A10

Bioethical Inquiry
DOI 10.1007/s11673-010-9208-8

From Evidence-based Medicine to Marketing-based Medicine: Evidence from Internal Industry Documents

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Received: 2 October 2009 / Accepted: 15 December 2009

Abstract While much excitement has been generated surrounding evidence-based medicine, internal documents from the pharmaceutical industry suggest that the publicly available evidence base may not accurately represent the underlying data regarding its products. The industry and its associated medical communication firms state that publications in the medical literature primarily serve marketing interests. Suppression and spinning of negative data and ghostwriting have emerged as tools to help manage medical journal publications to best suit product sales, while disease mongering and market segmentation of physicians are also used to efficiently maximize profits. We propose that while evidence-based medicine is a noble ideal, marketing-based medicine is the current reality.

Keywords Evidence-based medicine · Marketing · Marketing-based medicine · Pharmaceutical industry · Olanzapine · Quetiapine

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> The larger issue is how do we face the outside world when they begin to criticize us for suppressing data...
> *AstraZeneca publications manager in internal email 6 Dec 1999.*

According to conventional wisdom, we are firmly grounded in evidence-based medicine (EBM). While many forms of data, such as clinical experience, case studies, and uncontrolled trials can provide useful information regarding patient care, the randomized controlled trial (RCT) reigns supreme. As RCTs allow the direct comparison of drug and placebo or of various compounds to one another, their rigor exceeds that of other forms of research (Sackett et al. 1996). As more and more RCTs are published in medical journals, we gain a better understanding of what works best. Interventions that fail to demonstrate adequate efficacy and safety lose first line status and are discarded over time. Patients, of course, benefit immensely from this meticulous scientific evaluation process, as they can rest assured that they are receiving treatments that show the greatest benefit and least risk. So the story goes. However, one could argue that rather than EBM, we are actually now entrenched in *marketing-based medicine* (MBM), in which science has largely been taken captive in the name of increasing profits for pharmaceutical firms. The case for MBM is based on several factors, each of which influences the knowledge and practice of medicine, including: suppression and spinning of

Published online: 21 January 2010

negative data, ghostwriting, disease mongering, market segmentation of physicians, and failure of regulatory authorities and peer-reviewed journals (despite increasing efforts) to police what, in the words of Marcia Angell, former chief-editor of the New England Journal of Medicine, is a "broken system" (Angell 2008, 1069).

Richard Smith, former chief-editor of the British Medical Journal, in a paper titled "Medical journals are an extension of the marketing arm of pharmaceutical companies" described the many and sophisticated ways in which drug trial data can be manipulated. He said it took "almost a quarter of a century editing for the *BMJ* to wake up to what was happening" (Smith 2005, e138). Such manipulation was indeed difficult to discern in the past, but the release of internal pharmaceutical industry documents has shed light on how marketing has come to trump science (e.g., Applbaum 2008; Steinman et al. 2004).

These documents have been released by courts where pharmaceutical companies have been subject to litigation from class action plaintiffs and government prosecutors. They allow for close examination of many practices that are not typically widely publicized. Indeed, although many internal industry documents are legally available on the internet, there are as yet few publications in the biomedical literature based primarily on internal industry sources. These internal documents, as well as material drawn from other sources, provide insight into the intersection between marketing and science within the pharmaceutical industry. While the documents examined in this paper reflect our specialties in mental health, the manipulation of drug trial data they expose are clearly not limited to only this field, as evidenced by situations involving medications for osteoporosis (Washburn 2005) or non-steroidal anti-inflammatory agents (Ross et al. 2008; Smith 2006).

Science as Marketing

Especially given the current focus on using evidence-based treatments, it comes as no surprise that the pharmaceutical industry values scientific data that demonstrate efficacy and/or safety of their products. These data are particularly valuable when translated into articles in high impact peer-reviewed journals. A pharmaceutical industry trade publication emphasized this point. It mentioned that a good publication plan "targets such information toward highly reputable, peer-reviewed journals (which are today viewed as the single most trusted source of information by US physicians, over that of continuing medical education, thus enhancing its scientific imprimatur, while building relationships with the journals and their readership)" (Scarpuzza undated). Similarly, one memo from Pfizer asked "What is the purpose of publication?" and responded with "High quality and timely publications optimize our ability to sell Zoloft [the antidepressant sertraline] most effectively" (Clary 2000). The same document makes it clear that the data from sponsored drug trials belongs to the company and the "purpose of data is to support, directly or indirectly, marketing of our product" (see Fig. 1).

PeerView is a company that provides various services to the pharmaceutical industry, including "... products that support publication strategy and other commercialization processes for our pharmaceutical and biotech clients". The CEO of PeerView stated that "...most pharma and biotech companies recognize the significant impact that the clear and consistent publication of results will have on subsequent commercialization efforts" (Villarroel 2007, 2). An Eli Lilly internal document refers to new strategic planning for the branding of its antipsychotic drug olanzapine (Zyprexa). The document states under "strategic imperatives," that a goal is to "develop scientific research and publication plan that enhances credibility of the new brand positioning and enables the achievement of the ideal positioning" (Eli Lilly 2001a). To help meet this goal, it is mentioned that the company should "mine existing data to generate and publish findings that support the reasons to believe the brand promise" (Eli Lilly 2001a).

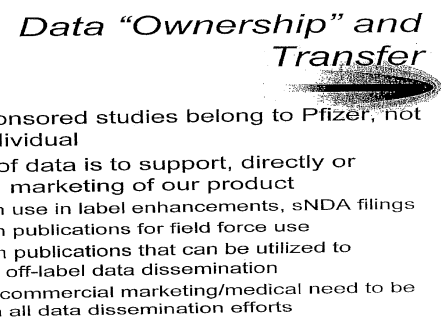


Fig. 1 Excerpt from document regarding marketing of sertraline (Pfizer)

Science is clearly related to marketing goals, which of course is not necessarily problematic. If a product is supported by good data, then few would find it unethical to disseminate such information. But what if the science is *not* supportive; what if a drug does not demonstrate efficacy or is dangerous? What if a study's results do not jive with the brand promise?

Suppressing and Spinning Negative Data

While drugs still enjoy patent protection, pharmaceutical companies typically provide the lion's share of the funding to investigate their products. Journal articles that tout the positive features of a drug help to keep product moving from pharmacy shelves. The data which form the backbone of these articles is controlled by the sponsor. It is well-known that studies funded by a drug manufacturer are much more likely to yield positive results than studies of the same drug conducted by researchers not tied to the sponsor (Lexchin et al. 2003). One main reason for this finding is that drug manufacturers are under no obligation to publish negative results. Indeed, if the primary goal of publicly traded drug firms is to maximize return to shareholders, it makes no sense at all to publish results that cast a drug in a negative light.

Quetiapine: Internal vs. Published Data

AstraZeneca's antipsychotic drug quetiapine (Seroquel) is one of a class of drugs known as atypical antipsychotics or second-generation antipsychotics. In 2000, data comparing quetiapine to haloperidol, an older, generic antipsychotic, were presented at the annual convention of the American Psychiatric Association. In a press release, the author of the presentation stated: "I hope that our findings help physicians better understand the dramatic benefits of newer medications like Seroquel, because, if they do, we may be able to help ensure patients receive these medications first" (Olson 2009). The presentation, in line with the press release, shows that quetiapine possessed a statistically significant advantage over haloperidol in inducing treatment response among patients with schizophrenia. These data were based on a meta-analysis of four studies that compared quetiapine and haloperidol. However, documents released by the company during litigation suggest a quite different story. The results of research comparing the two compounds are found in an AstraZeneca document, in which it was concluded that quetiapine possessed *weaker* efficacy than haloperidol (AstraZeneca 2000; see Fig. 2). The company document was produced in March 2000, two months prior to the rosy presentation of quetiapine's efficacy. An email regarding this data, from a publications manager at AstraZeneca, stated in part: "The data don't look good. In fact, I don't know how we can get a paper out of this" (Tumas 2000; see Fig. 3). The lead researcher on the 2000 paper, when queried recently by a journalist regarding the claim that quetiapine is "significantly superior" to haloperidol, conceded that the claim was indeed an exaggeration yet maintained that the data analysis was accurate (Olson 2009).

AstraZeneca also commissioned a comparative trial known as Study 15. In this trial, patients in partial to full remission of schizophrenia were randomly assigned to receive either haloperidol or quetiapine. At the end of the one-year trial, patients receiving haloperidol fared better in terms of symptom ratings and had significantly fewer psychotic relapses relative to patients on quetiapine. These negative results were not published. Rather, as stated in an internal email, "cherry picking" occurred (Tumas 1999; see Fig. 4). On some measures of cognitive functioning, quetiapine significantly outperformed haloperidol, which was the basis for a publication (Velligan et al. 2002). The abstract included the statement: "Treatment with quetiapine at higher doses relative to haloperidol appears to have a positive impact on important domains of cognitive performance that have been found to predict role function and community outcomes in patients with schizophrenia" (239). While the paper suggested the likelihood of better community outcomes, it failed to mention the increased risk of psychotic relapse and the relatively poorer scores on symptom measures compared to haloperidol. In an internal email two other "buried trials" are mentioned, in addition to a third trial that was pending potential suppression at the time of the message (Tumas 1999).

Antidepressants: Internal vs. Published Data

Such tactics are not unique to any individual company; they are quite plainly widespread. Indeed,

Fig. 2 AstraZeneca internal meta-analysis of quetiapine vs. competitors/placebo

The following table is an attempt to simplify the claims that could be obtained from these results. A ✓ is entered for those comparisons where we have a statistically significant benefit, be it with 'all doses' or with high dose Seroquel, and be it using observed cases or using LVCF. A ✗ marks those comparisons where a comparator has demonstrated significant superiority compared to Seroquel.

Table 1

Comparator	Category						
	Anxiety	Total BPRS	Factor I	Factor V	Hostility	Hostility Cluster	Mood Cluster
Placebo	✓	✓	✓	✓	✓	✓	✓
Haloperidol	-	✗	-	✗	-	✗	-
Chlorpromazine	-	-	-	-	-	-	-
Risperidone	✗	✗	✗	✗	-	✗	✗
Other typicals	-	✗	-	✗	-	✗	-

one investigator calls data suppression "the dirty little secret" of medical research (Dawdy 2008). The researcher, Erick Turner, led a team which compared published trials of antidepressants versus their unpublished counterparts. Pharmaceutical firms must submit their clinical trial data to the Food and Drug Administration (FDA) as part of their application for approval for marketing the drugs in the United States. Turner's team examined the publication status of trials submitted to the FDA for all antidepressants approved by the agency from 1987 through 2004 (Turner et al. 2008a).They found that 97% of the trials in which the FDA review found a positive outcome were then published in a journal. Some trials yielded a "questionable" outcome, in which the data on the primary outcome was negative but some secondary measures found the drug was efficacious. Half of the trials in which the FDA review found a "questionable" outcome were published and half were not. Of the "questionable outcome" trials that were published in a medical journal, all were written up as if the results were positive. Only one-third of studies finding negative results were published, and over half of those were published claiming that the study actually found positive outcomes.

How can a trial go from showing questionable or no efficacy to a definitive statement of efficacy? Various publications did the following: failing to report data from all participants (those who dropped out due to lack of efficacy or adverse events were excluded), reporting data from only one site of a multisite trial, reporting data for something called an "efficacy subset," which is an apparent euphemism for scrubbing inconvenient data from the dataset, and by switching primary outcomes post hoc (Turner et al. 2008b). For each of the 12 antidepressants, at least one trial was unpublished or at least one trial was published with conclusions conflicting with FDA review of the data. Thus, one cannot blame one or two "bad apples," as it appears data suppression is part of the industry's standard operating procedure.

Fig. 3 AstraZeneca email regarding meta-analysis of Seroquel vs. competitors/ placebo

From: Tumas John JA
Sent: Thursday, March 23, 2000 10:05 AM
To: Goldstein Jeffrey JM; Murray Michael MF
Subject: FW: Meta Analyses
Importance: High

Jeff and Mike,

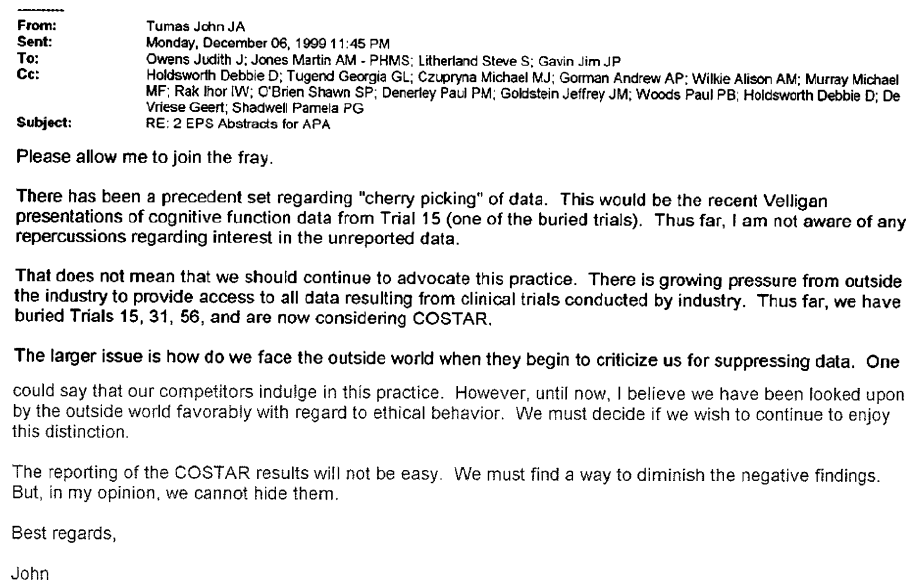
Here's the analyses that I got from Emma. I've also attached a message that I sent to her yesterday asking for clarification.

The data don't look good. In fact, I don't know how we can get a paper out of this.

My guess is that we all (including Schulz) saw the good stuff, ie the meta analyses of responder rates that showed we were superior to placebo **and** haloperidol, and then thought that further analyses would be supportive and that a paper was in order. What seems to be the case is that we were highlighting the only good stuff and that our own analysis support the "view out there" that we are less effective than haloperidol and our competitors.

Once you have a chance to digest this, let's get together (or telelconference) and discuss where to go from here. We need to do this quickly, because Schulz needs to get a draft ready for APA and he needs any additional analyses we can give him well before then.

Thanks.



From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

Fig. 4 AstraZeneca email regarding "cherry picking" and "suppressing data"

Along the same line, data were selectively published regarding antidepressant use among children and adolescents (Whittington et al. 2004). One notable example is a study (known as Study 329) comparing paroxetine (a serotonin-reuptake inhibitor antidepressant, manufactured by Smith Kline Beecham (SKB) which is now GlaxoSmithKline (GSK) under the brand name Paxil), imipramine (an older, tricyclic antidepressant), and placebo in the treatment of adolescent depression. Study 329, sponsored by SKB/GSK, was published in 2001 with a clear message stated in the abstract: "paroxetine is generally well tolerated and effective for major depression in children" (Keller et al. 2001, 762). However, the trial data indicated that the drug was neither efficacious nor particularly safe.

How did this come about? During litigation, GSK released documents concerning the study, which were then compared with the published version. The study protocol and its revisions named two primary outcome measures but both failed to demonstrate a significant advantage over placebo at study endpoint. The original study protocol also had six secondary measures, all of which likewise failed to show efficacy. In the published version of the study, four of eight measures were reported as positive (rather than zero of eight)—all were on measures not called for in the study protocol or revisions, a classic case of data fishing.

The study publication referred to six of 93 paroxetine participants compared to one of 87 placebo participants experiencing "emotional lability," (a term used to describe "suicidal ideation/gestures"). An internal company report of side effects of paroxetine yields more—eight participants experienced suicidal gestures or deliberate self-harm and seven cases of hostility on paroxetine compared to zero on placebo. An earlier draft of the results stated that "worsening depression, emotional lability, and hostility were considered related or possibly related to treatment," yet the published version claims that only one case of headache was considered related to paroxetine. Thus, a drug failed to demonstrate efficacy on all eight pre-specified primary and secondary efficacy measures, is related to more treatment-emergent suicidal gestures and hostility, and yet is claimed in a peer-reviewed journal to be safe and effective (Jureidini et al. 2008).

Internal discussion about whether the company should even publish the study included an email that read: "originally we had planned to do extensive media relations surrounding this study until we actually viewed the results. Essentially the study did not really show Paxil was effective in treating adolescent depression, which is not something we want to publicize" (White 2001). Nonetheless, the study was published and, in an internal document distributed to all company representatives selling paroxetine, was labelled a "cutting-edge landmark study" demonstrating "REMARKABLE" efficacy and safety for the drug (Hawkins 2001).

Ghostwriting

Publications provide important information regarding drug safety and efficacy. These articles are probably most influential when they are perceived as independent from the drug company. A physician may view an article with a corporate authorship line as biased yet view the same article as more credible if independent academic authors were listed as contributors. However, academics are often busy with research obligations, speaking engagements, teaching, administrative duties, clinical work and other tasks and some are not particularly skilled at writing. Ghostwriting overcomes these limitations. A pharmaceutical firm may design a paper in-house or contract with a medical education and communication company (MECC) to write a manuscript.

Writing Firms

One example is Sunvalley Communication (http://sunvalleycommunication.com). Their website describes several important services (Hofland undated). They produce papers closely linked with "brand strategies" and also create a publication strategy to "align with marketing strategy" and "tweak" their message to best suit the publication and target audience. This firm also offers to compose papers for researchers and graduate students based on an outline provided by the researcher—and its involvement can be "strictly confidential" (Sunvalley Communication undated). Another company, Dianthus Medical, receives "key messages" from pharmaceutical clients and writes a manuscript outline, which they recommend receives approval from all authors who will be listed on the paper. They then write the first draft of the paper, "ensuring that your message is communicated in the most effective way," then pass it along for the client's approval. Revisions are made and the paper prepared for submission to the journal (Dianthus Medical undated). This company lists such pharmaceutical giants as AstraZeneca, GlaxoSmithKline, Lilly, and Wyeth among its clients. Sunvalley and Dianthus are but two of many such companies; descriptions of similar firms have been provided elsewhere (Sismondo 2007).

The process is relatively simple: A ghostwriter includes messages to maximize the marketing power of the publication while one or more "honorary" academic authors lend their names, titles, and purported independence to the paper (Moffat and Elliott 2007). While the audience may look suspiciously on a paper with an all-corporate authorship line, the presence of an academic author lends the air of independence and prestige, making the article appear more credible. The academic authors may review an outline or draft, but typically perform little writing. For example, an internal Eli Lilly document discusses "drafting a full feature for review" by an influential author or perhaps having the author develop the article after reviewing the outline provided by the company or its associated writing firm (Eli Lilly undated-a).

Ghostwriting in the Antidepressant Literature

The prevalence of ghostwriting is obviously hard to determine. A few studies have suggested that approximately 10% of papers are ghostwritten, but these are based upon self-report surveys, which likely under-report the incidence of such behaviour (Flanagin et al. 1998; Mowatt et al. 2002).

Through litigation, one research team gained access to documents regarding the antidepressant sertraline (Zoloft)—remember that according to its manufacturer, publications were primarily meant to maximize sales of this drug. A MECC named Current Medical Directions (CMD) contracted with Pfizer to produce 85 publications regarding the drug. According to one analysis, between 18% and 40% of articles on sertraline from 1998–2000 were managed by CMD (Sismondo 2007). The majority of the CMD articles featured academic authors—one author appeared in 12 such publications. In addition, the articles managed by CMD appeared in significantly higher-impact journals compared to non-CMD articles on sertraline. One document from CMD lists a number of sertraline publications in various stages of completion—several contain notes such as "Author TBD"—indicating that while a medical writing firm was completing (or had completed) the paper, a so-called "author" had yet to lend his or her name to the piece. Other notes include such comments as "outline sent to Pfizer for approval" (Current Medical Directions 1999).

Researchers who investigated the CMD-affiliated articles made the crucial point that traditional science relies on authors having access to the underlying raw data that forms the basis of publications (Healy and Cattell 2003). However, publications written by drug

firms or MECCs are often based on proprietary data belonging to the drug firm. If an academic author cannot vouch for the underlying data and did not write the paper, then how can he or she be anything other than window dressing for a marketing device wrapped in scientific packaging? Healy and Cattell (2003) note that a case of completed suicide and several cases of suicidal ideation were not reported in the CMD-authored pieces. The first draft of the paper from Study 329, which clearly overstated benefits and understated risks, was also written by a MECC (McHenry and Jureidini 2008). The lead author of the study said that he only reviewed data tables, not the raw data (BBC 2007). Thus, honorary academic authors are not just padding their vitae, they are also potentially harming public health when they fail to carefully review data presented in studies on which their names appear as authors.

While honorary authors are typically affiliated with universities, non-academic clinicians are also sometimes utilized to author papers in an unconventional manner. GlaxoSmithKline used such a program to promote its antidepressant paroxetine (Paxil). The plan, which used the interesting acronym "CASPPER—Case Study Publications for Peer Review" had the following main goal: "Publications of such articles will benefit the sales force by expanding the database of published data to support Paxil" (SmithKlineBeecham undated). If a physician mentioned a success with paroxetine, sales representatives were to encourage the physician to write a case study. Sales reps were instructed to acknowledge the importance of the physician's time and offer to save precious time through the contracted editorial staff, who could assist with everything from literature searches to editing the paper. It seems that physicians had relatively little leeway regarding their papers—one excerpt from a company document stated that the editorial team would "work closely with contributing physicians to ensure rapid dissemination of consistent data and messages". It is likely that data inconsistent with the company's marketing was not part of the publication plan. At least five journals reportedly published papers produced through CASPERR (Edwards 2009a).

Placebo-controlled trials often include a placebo wash-out phase, in which all participants initially receive placebo prior to some participants then switching to the drug under investigation. For example, a study may use a 3-week period of placebo washout, followed by 8 weeks of patients receiving either drug or placebo. It should be obvious that the comparison of efficacy and safety between drug and placebo should begin during the fourth week, when half of the participants have started receiving active medication. Yet some manufacturers of antidepressants counted suicidal behaviour in the placebo wash-out phase against placebo in their comparisons of drug to placebo. Comparing suicidal acts on 11 weeks on placebo to 8 weeks on a drug helped to drive up apparent rates of suicidal behaviour on placebo, which made the drugs appear safe in comparison. Indeed, an article was published in 1995 allegedly showing that paroxetine reduces suicidality. The academic author admitted that he had not seen the actual raw data; rather, he had been provided data tables by the manufacturer, which he then helped to convert into an article (Glenmullen 2007). However, the data in the article included suicide attempts which occurred during the placebo washout phase, though this was not stated in the manuscript. GSK has since posted its own analysis online, in which it notes an increased risk of suicidal behaviour among patients taking paroxetine relative to placebo (GlaxoSmithKline undated). Nearly anyone reading a journal article will assume that the named authors had access to raw data rather than misleading data tables provided by a drug firm. While not technically ghost authorship, the manner in which the data were translated into final form is clearly outside of the norms of science.

Investigator-initiated Trials and Opinion Leaders

Further evidence on the extent that companies, rather than honorary authors, own and manage drug trial data comes from an internal AstraZeneca email from the "Global Brand Manager—Seroquel" (quetiapine) to the "SEROQUEL GLOBAL BRAND TEAM" dated "8/7/2003" on the subject "IIT benchmarking report" (Hagger 2003). IIT stands for "Investigator-initiated trials" where an academic or clinician from outside the company is sourced as author of the trial. This email refers to a "series of interviews carried out with internal AZ staff who were known to have worked for competitor companies before as well as a number of KOL [key opinion leader] investigators from the UK, Italy, Germany

and Spain." The email lists "key messages emerging from the report:

- ...Lilly run a large and highly effective IIT program...They offer significant financial support but want control of the data in return. They are able to spin the same data in many different ways through an effective publications team. Negative data usually remains well hidden.
- Janssen have a well organized IIT plan...no IIT data is allowed to be published without going through Janssen for approval, and communication is controlled by Janssen. High expectations are set on investigators who publish favourable results but they are well rewarded for their involvement. They seem less concerned than Lilly about negative data reaching the public domain.
- BMS IIT program is growing very fast in launched markets...most proposals are modified by BMS. Strategic focus is unlicensed indications...

Recommendations...for AstraZeneca...publications should be more creative spinning the data, aka Lilly..."

In fact an Eli Lilly document on "influencing key players" in a passage headed "Investigator-Initiated Trials, Relationship Building, and External Authorship", states:

> Given our current business needs, it is important that funds spent on IITs predominantly support the brand strategy. The review process should consider whether they are on strategy, as well as looking at whether they fill current gaps in our scientific data (Eli Lilly undated-b).

KOLs with the right message can be very valuable to a company. An August 2002 email reporting on a Janssen-sponsored dinner presentation on metabolic side-effects of atypical antipsychotics in which a speaker "consistently implicated (Zyprexa) as a likely cause of type 2 diabetes or cardiac problems via weight gain" noted "I think if I were with J [Janssen], I'd be throwing some cash at this chap to get his message more widely known" (Eli Lilly 2002a). The Eli Lilly "Key Player Playbook" ranks contracted academic experts as "Guild and Executive level Thought leaders" who "are well respected and acknowledged by their peers...influence the thinking and treatment practices of their peers...and are typically in the academic setting and treat a minimal number of patients, if any...and serve on academic advisory boards, providing feedback to the Zyprexa Product and Brand Team" (Eli Lilly undated-b). Next in rank are "Consultant Thought Leaders...who are a critical component of successful DTP (direct to physician i.e. sales rep) interventions and stimulate the physicians at both the regional and the local level". A September 2000 letter from a psychiatrist who was "one of our (Eli Lilly) speakers" on off-label use of olanzapine by primary care physicians suggested the local thought leader understood his role very well:

> ...Once the ground is extensively plowed with good credible clinical information, not limited by the GPP [Good Promotional Practice] guidelines that restrict information to schizophrenia and acute mania, then (perhaps) turning the sales force loose may be appropriate. I believe one of my strengths is in taking scientific information and placing it in a clear, clinically useful format...Lilly could use someone with a strong clinical background but with strong marketing instincts to assist them on this one (Eli Lilly 2000a).

Safety: Science or Marketing?

Weight gain, hyperglycaemia and precipitation of diabetes have been major concerns in the side effect profiles of atypical antipsychotic medications. Internal company documents from Eli Lilly and AstraZeneca have a significant focus on the marketing management of these side effects.

Olanzapine: Managing Perceptions of Side Effects

The transcript of a speech by the olanzapine (Zyprexa) Brand Manager stated: "For Zyprexa, weight gain is the ultimate topic to handle with skill. Take this opportunity to tell the truth, to fight fire with facts and to put this manageable side effect in perspective. Keep it simple, so that you don't overwhelm the doctor with data" (Bandick 2001). Industry documents, read as a whole, give a strong impression that ensuring adverse events "not overwhelm the doctor" means telling the doctor the bare minimum about them.

Eli Lilly had been aware that "forty percent [on olanzapine] gained ≥7% body weight" (the FDA's level of "significant concern" for weight gain) from at least an early trial—the HGAJ study—reported in minutes of a meeting with the US schizophrenia advisory panel in December 1995 (Eli Lilly 1995). The company received a letter of reprimand from the FDA in November 1996 reminding that "the information on weight gain was indeed included in the approved labelling, but as an adverse event, not a therapeutic benefit" (Feather 1996). An internal email among senior science executives in Eli Lilly dated 24 November 1999, "subject: Olanzapine-associated Weight Changes (OWC)" noted that, "...OWC has been and continues to be a top priority for the Zyprexa Product Team". The email went on to state: "Olanzapine is viewed to have more associated weight gain than risperidone, seroquel, and traditional neuroleptics (Fact: the order of weight gain among antipsychotics is: Clozapine>olanzapine> seroquel>risperidone>traditional neuroleptics)". The email noted "Physicians want more data" but also, "Blanket detailing will be damaging since many physicians do not see OWC as an issue" (Breier 1999).

Despite this early recognition that olanzapine caused more weight gain than other antipsychotics apart from clozapine, the marketing message for sales visits and CME became the "comparable rates" or "class side effect" message—olanzapine was no different than other atypical antipsychotic agents in inducing weight gain or diabetes (Eli Lilly undated-c; Eli Lilly 2000b; see Figs. 5 and 6). A September 2001 hyperglycaemia/diabetes resource guide for sales reps states:

> What do we mean by "neutralizing" physicians' concerns about hyperglycemia and how do we go about this? By neutralizing we mean levelling the playing field, setting the record straight with the "comparable rates" message (Eli Lilly 2001b).

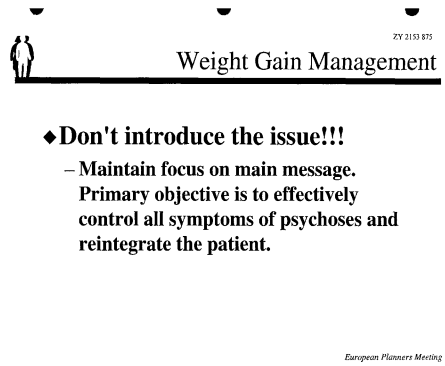


Fig. 5 Eli Lilly instructions to sales reps regarding weight gain issue

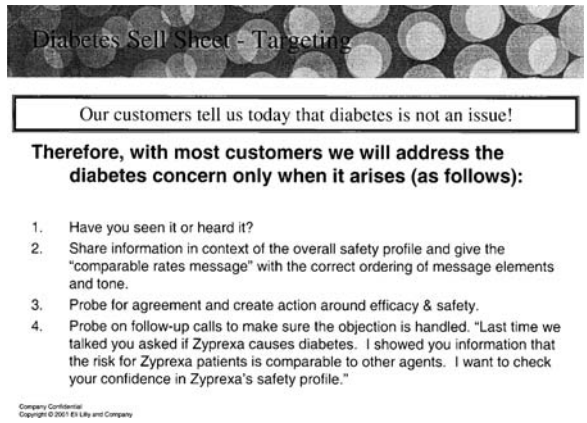


Fig. 6 Olanzapine diabetes sell sheet excerpt

Documents reveal Eli Lilly wanted to keep weight gain and diabetes as separate issues that were not linked. An undated review of "Olanzapine core safety and efficacy beliefs" stated: "A causal link between Olanzapine therapy and diabetes has not been established" (Eli Lilly undated-d). However, the same document also noted: "A potential reason for this is that most of our studies were not designed (especially given the relatively short duration of these studies) to study a link between Olanzapine therapy and Diabetes". Documents reveal the company was in receipt of letters from psychiatrists describing anecdotal reports of high rates of hyperglycaemia and diabetes from olanzapine, such as a letter dated 17 November 1999 stating: "we have had eight patients out of possibly 35 on Zyprexa show up with high blood sugars...we certainly have never seen this with Haldol, Navane, Risperdal, and others to this extend [sic]" (Ventura County Behavioral Health Department 1999). An early report of data on adverse events from placebo-controlled trials of olanzapine stated in larger font than the rest of the document:

> As of September 30, 1999, olanzapine-treated patients (N=4,234) who had no history of diabetes mellitus and whose baseline random plasma glucose levels were 140 mg/dL or lower were identified. Random glucose levels ≥160 mg/dL but <200 mg/dL (possibly hyperglycemia, not necessarily diabetes) were observed in 2% of

> patients. Of these patients, the random elevated glucose levels were found to be transient in 44% while they continued to receive olanzapine. Random glucose levels ≥ 200 mg/dL (suggestive of possible diabetes) were observed in 1% of patients. Of these patients, the random elevated glucose levels were found to be transient in 26% of them while they continued to receive olanzapine (Eli Lilly undated-e).

In other words, despite the short-term nature of most of these trials, 3% of patients were exhibiting possible new onset hyperglycaemia or diabetes and a proportion of them reverted to normal when olanzapine was withdrawn. The fact that hyperglycaemia was reversible at least if caught early was not appreciated by one Eli Lilly company psychiatrist, who responded in an October 2002 email: "But, surely we want patients to stay on OLZ long-term, so the reversibility of the event is not an advantage?" (Williamson 2002).

An internal email dated "12/01/98" on "Subject: Re: Wishing/Goldstein articles" stated:

> I do have concerns regarding making any connections between olanzapine-induced weight gain and hyperglycemia. Therefore, in my opinion, I would not include your following statement: "Patients who gain weight may develop insulin resistance which may lead to hyperglycemia and diabetes" (Kinon 1998).

By September 2000 Eli Lilly's own market research revealed that many more physicians (81%) associated "increased risk of diabetes with...Zyprexa" than with other agents—Clozaril (56%), Risperdal (16%), Haldol (11%), Mellaril (11%), Seroquel (7%), Tercian (4%) (Phoenix International Research 2000). An internal email to 15 company scientists and executives from October 2000 on "Subject: meeting with endocrinologic consultants" noted "at least the vocal" endocrinologists were disputing the company's "finding that relative risk was not higher than comparative drugs" and "reinforced (the writer's) impression that hyperglycemia remains quite a threat for olanzapine and may merit increasing even further medical attention and marketing focus on the topic" (Baker 2000). A reply email revealed a growing debate within the company "that unless we come clean on this...issue that Zyprexa leads to diabetes...it could get much more serious than we might anticipate" and urged "gaining the ear of senior leadership and articulating this finding" (Brodie 2000).

Nonetheless the company still held to the marketing strategy of "comparable rates" and a December 2000 "diabetes situation analysis" on "Market Research on 'message'" reported the "comparable rates" message "appears to be generally believable, makes 'em think but not all MDs change their basic premise" (Eli Lilly 2000b). The message to the sales reps was still the same in a September 2001 hyperglycaemia/diabetes resource guide:

> Market research has shown that ALL of our competitors are talking about a supposed link between hyperglycemia/diabetes and ZYPREXA. This is one of the biggest issues we face in the marketplace. The exciting thing is that we have more data than ever to back up our story of "comparable rates of hyperglycemia and diabetes across psychotropic agents." It is critical to our success that we share this information with physicians (Eli Lilly 2001b).

Internal documents addressed to sales reps mostly refer to physicians, pharmacists and other health professionals as "customers". The September 2001 resource guide went on to note: "For tough customers, the use of the Hyperglycemia Sell Sheet followed by the Study Comparison Insert increased the believability of the 'comparable rates' message" and concluded: "Customers require lots of repetition for message recall and true behaviour change". Slides from 2001, to be used in sales rep training reflected that minimizing discussion of hyperglycaemia/diabetes where possible was company sales strategy (Eli Lilly 2001b; see Figs. 6 and 7).

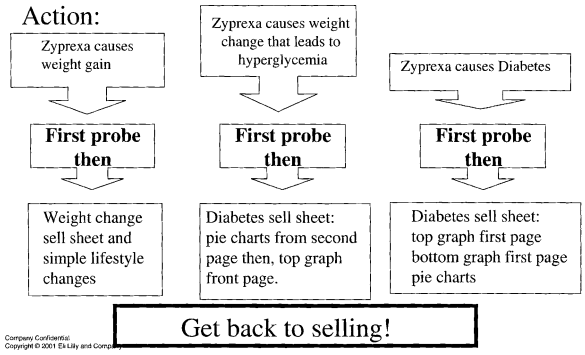


Fig. 7 Excerpt from olanzapine sales representative training material

A series of emails in March and April 2002 reveal that Eli Lilly was extremely keen to avoid regulatory product information label changes "to not use Zyprexa in patients with diabetes or a history of diabetes" and "contain a warning statement that some patients may experience a marked increase in blood glucose during Zyprexa administration" as proposed by Japanese regulators (Cavazzoni 2002a, b; Kerr 2002). A verbatim statement was drafted on the issue that "Lilly's fundamental position regarding incidence of hyperglycemia and/or diabetes across antipsychotic class continues to be 'comparable rates'" and further that "Lilly stands by its science, and is exploring several options to correct this regulatory injustice". But the issue persisted and by November 2002 an email on the Japanese label issue stated: "What is the strategy regarding diabetes? Are we trying to show through retrospective studies that it isn't that big of a problem? I understand that we are trying to neutralize the issue, but how are we trying to do that?" (Aubuchon 2002). On 15 September 2003 Eli Lilly "received letter from FDA requesting inclusion of warning regarding hyperglycemia and diabetes in labeling" for the US market (Eli Lilly undated-f).

By January 2004 the Eli Lilly "Weight Task Force" suggested "A major change in tone and approach is required (empathic with conviction) to restore confidence...weight gain will no longer be handled as an objection. Instead weight gain will be discussed up front, integrated into the brand promise" (Eli Lilly 2004). Nonetheless a December 2003 PowerPoint presentation for the sales reps concerning "managing weight gain and diabetes concerns" suggested a less empathic approach (Eli Lilly 2003; see Fig. 8).

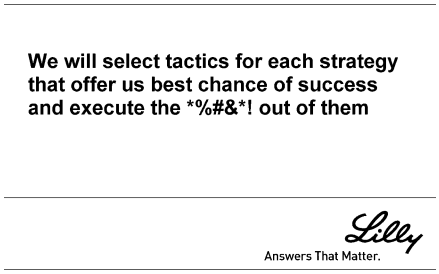


Fig. 8 Excerpt from olanzapine sales rep training for managing customer (physician) concerns regarding weight gain and diabetes

Quetiapine: Managing Side Effects

In a somewhat similar manner, data regarding weight gain on quetiapine were managed by AstraZeneca. One internal document, titled "Seroquel Speakers Slide Kit" from March 2001, was apparently utilized to educate physicians regarding the safety and efficacy of the drug (AstraZeneca 2001). One slide makes the claim, in bold, that "Long-term Seroquel has neutral effect on weight," while another stated "Seroquel—weight neutral at all doses". Several other slides make similar claims. These slides were based on studies examining the drug in the treatment of schizophrenia. Another set of slides, included in a 2003 email, were said to "represent a core detail flow" to "support our current position for Seroquel in the treatment of schizophrenia". One slide stated that: "Seroquel, unlike some other antipsychotics, is not associated with meaningful weight gain" (AstraZeneca 2003).

Yet in July 2008, an internal analysis of quetiapine studies in schizophrenia conducted from 1993 to 1999 concluded that "the incidence rate in adult patients with weight gain ≥7% in all trials was 18.2%" and that in placebo-controlled trials, the relative risk of clinically significant weight gain was 2.5 (Alam and Jeffries 2008). The document noted that "the results of the analysis show that long-term treatment with quetiapine monotherapy was associated with moderate weight gain in patients with schizophrenia". However, a journal publication in 2000, with a lead AstraZeneca author, concluded that based on data from clinical trials with patients with schizophrenia, quetiapine had a neutral effect on weight (Brecher et al. 2000). A physician practicing EBM may have examined this study and concluded that quetiapine was weight-neutral when the internal data indicated that weight gain was a common side effect of the drug.[1]

Despite marketing claims to the contrary, employees at AstraZeneca were concerned about quetiapine-induced weight gain as early as 1997. In one email, written regarding an apparently fluke study associating quetiapine with weight loss, an employee noted that "we

[1] One of the authors (PP) prescribed quetiapine to several patients due to its promotion as weight-neutral (based on publicly available EBM at the time) and was quite surprised when some patients experienced significant weight gain.

must not get too carried away with weight loss when we know the rest of our data appears to point in the other direction" (Hough 1999). In another email, a company physician who worked with quetiapine noted that trial results consistently found that, over time, weight gain "doesn't stop…the slope just appears to change" (Arvanitis 1997). A brief synopsis of several relevant documents on the topic of quetiapine and weight gain is available online (Edwards 2009b).

Disease Mongering

"Disease mongering" refers to the practice of expanding the recognised boundaries of a disease entity to encompass subclinical, borderline and normal range symptoms in order to increase prescriptions and sales for a drug or therapy (Moynihan et al. 2002). Internal industry documents concerning Eli Lilly's atypical antipsychotic olanzapine (Zyprexa) suggest the company saw the potential to increase sales not only by gaining indication for the management of all phases of bipolar disorder, but for utilizing marketing tactics that expanded the boundaries of the illness itself.

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). 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). 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*. A *true mood stabilizer* will work in acute manic episodes without inducing depression, acute depression without inducing mania, and protect the patient from future episodes of mania or depression". These are noble aims but the same document indicated the company did not yet have the data to support such a goal.

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 2002b). A slide featured in Fig. 9 shows 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," comprised of some combination of anxiety, disruptive sleep, irritability, and mood swings (Spielmans 2009). This new type of patient was a source of "untapped growth potential" for the drug. Additionally, fictional patient vignettes were created for sales reps that highlighted possible bipolar disorder or "complicated mood" in cases of relatively minor mood instability that did not meet current diagnostic manual (DSM-IV, ICD-10) criteria for bipolar disorder I diagnosis. These vignettes were to be used in sales visits to help physicians identify patients who might suffer from "complicated mood" symptoms. To handle objections from physicians who indicated they did not treat schizophrenia or bipolar disorder, a script read:

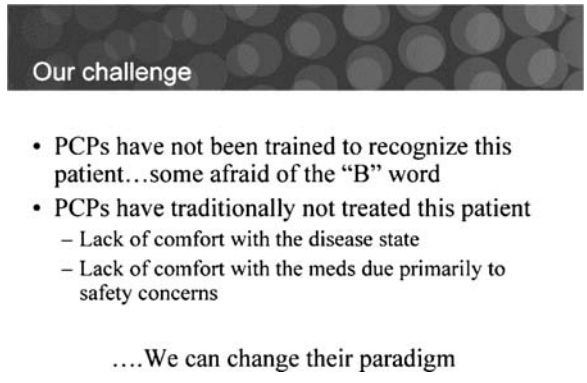


Fig. 9 Eli Lilly slide regarding perceptions of primary care physicians toward bipolar disorder

"Doctor, would you agree that you see patients who present with symptoms of mood, thought, and behavioural disorders who are not responding to your satisfaction" (Eli Lilly undated-g). Thus, physicians who worked with exceedingly few patients who met diagnostic criteria for olanzapine's indications were encouraged to simply look for patients who had *symptoms* as opposed to the full-blown disorder in question.

These documents, with reference to changing and expanding the diagnostic paradigm for bipolar disorder, are of great topical interest in the context of the current controversy over the boundaries of bipolar disorder (Paris 2009). Despite valid concerns of late diagnosis of bipolar disorder (Berk et al. 2006), there is evidence of overdiagnosis of bipolar disorder in recent years in adults (Goldberg et al. 2008; Zimmerman et al. 2008) and children (Carlson 2009; Healy and Le Noury 2007; Moreno et al. 2007). It seems quite likely that pharmaceutical marketing is related to the increasing rate of bipolar diagnoses (Zimmerman et al. 2008; Healy 2006; Healy and Le Noury 2007).

Market Segmentation

The lengthy Eli Lilly document titled "Key Player Playbook" provides insight into how marketing messages are tailored specifically to certain characteristics of a physician. Physicians were broken into five segments: Rule Bound, High Flyer, Skeptical Experimenters, Selective Majority, and Systematic Conservatives (Eli Lilly undated-a). At the time the document was written, olanzapine marketing was focused on High Flyers and Rule Bounds.

High Flyers were described as physicians who were defined by the statement "I eagerly seek out new ways to treat my patients (first to adopt new medicines)". These were the physicians on the cutting edge of medicine. Other descriptions of this segment of physicians were as follows:

- "Not bound by rules, guidelines, or system..."
- "Treat based on symptoms, not formal diagnosis"
- "Will push the envelope with off-label doses and indications..."

Based on this profile, olanzapine marketers were encouraged to utilize a few specific tactics to sell the drug. It was noted that High Flyers like to receive "pharmaceutical company sponsored programs and tools in 'fun' environments". They were also noted as being highly responsive to discussions with sales reps, likely because High Flyers viewed reps as "providing the source of latest information". It was also noted that they might like to become part of a forum/club, presumably formed by the company, to "reinforce NS [neuroscience] leadership in a social way". A skeptic might note that this technique could be taking advantage of a certain vanity believed to exist in the High Flyers, who would appreciate their "leadership" being recognized by a drug company.

To sell the exact same drug to a different group, the "Rule Bounds," a much different approach was recommended. While the High Flyers did not play by the rules, Rule Bounds were described as follows:

- "I follow the rules when treating my patients; if you don't follow the rules, you'll pay for it later"
- "Diagnosis clearly determined for treatment"
- "Wait to use medication when well established in the system"

Rule Bounds were to be reassured that they were following treatment guidelines. It was advised that Rule Bounds should be placed with physicians who could discuss "what everyone is doing". It seems likely that the other physicians would be carefully selected by Lilly to make sure to describe olanzapine as the drug that "everyone" is prescribing, thus catering to the tendency of Rule Bound physicians to use "well-established" medications. Another document cited the company's "superior recruiting capabilities so the right doctors go to the right programs," then referencing both sales rep visits and "peer-to-peer" marketing, where physicians would market the drug to their peers (Eli Lilly 2002c).

The other types of physicians (Skeptical Experimenters, Selective Majority, and Systematic Conservatives) were perceived as less likely to respond to marketing than Rule Bounds and High Flyers. Thus, marketing resources were targeted toward the most easily influenced physicians, enabling Eli Lilly to achieve a greater return on its marketing investment.

Potential Remedies

MBM likely leads to poorer outcomes and increased costs. The time is ripe to reform how data from

pharmaceutical trials are disseminated. Clearly, better access to raw data is needed. Clinical trial registries have not solved the problem; even among trials which appear in such registries, selective reporting of outcomes is common (Mathieu et al. 2009). Editors, peer reviewers, and readers of trial results should check online registry entries to verify whether the data in a published clinical trial match the results and protocol in the registry. In addition, public access to regulatory agency reports would also be useful, as there is often a notable discrepancy between data received by regulatory agencies and data published in medical journals (e.g., Turner et al. 2008a). Public access to both trial protocols and results would greatly increase transparency and allow physicians and consumers to better assess the validity of clinical trial results (Chan 2008).

More radical methods have also been proposed. A former editor of *BMJ*, Richard Smith, suggests that journals should cease the publication of clinical trials. Rather, trial protocols and results could be published in some form of online registry. Journal articles would then discuss the validity of these trials. This may seem like an odd solution, but there is in fact little evidence that peer review is linked with notably better reporting of trial results (Jefferson et al. 2007). Reprints of trials with ostensibly positive results are often disseminated to prescribers, a marketing strategy that one large biomedical journal publisher calls "invaluable for direct marketing, exhibitions/seminars, sales campaigns, and for mailing new product information to physicians" (Elsevier 2007). Further, reprints generate revenue for journals; thus, Smith claims that editors may feel pressured to publish trials that could make profits for the journal's publisher regardless of the trial's quality (Smith 2005). Indeed, Smith estimated that one especially profitable reprint used to market the now disgraced painkiller rofecoxib generated about $450,000 for the publisher (Smith 2006). Such conflicts of interest could be eliminated if journals no longer published clinical trials. However, it seems unlikely that publishers would want to reduce their profitability by simply giving up publication of clinical trials. These reforms may seem drastic, but if we are truly interested in providing the most safe and effective treatments to patients, then the actual scientific evidence regarding treatments must be made publicly available.

Conclusion

Internal industry documents allow a glimpse into the shadowy world of MBM, where data serve the needs of marketing and inconvenient data are often recast as positive or buried entirely. If, on the other hand, we are to fulfil the worthy ambitions of EBM, all data collected in clinical trials would be easily accessible. Journal articles would accurately represent the underlying data and individual contributors to a study would be given credit for their role in conducting research. Marketing efforts would contain accurate information. However, in the current world of MBM, journal articles are an overly positive representation of safety and efficacy, articles are often prepared by drug marketers (whose influence is hidden by honorary authors), marketing efforts contain misleading information about both diseases and treatments, and physicians are partitioned into market segments in order to best persuade them to believe various marketing pitches. Until such issues are resolved, particularly those regarding widespread access to accurate data, any great enthusiasm for so-called evidence-based medicine should be viewed with scepticism.

Limitations

The industry argues in court that subpoenaed documents are taken out of context. This should be considered by readers of the above excerpts. A fuller picture is available from reading the many documents released and posted on the internet (e.g., http://www.furiousseasons.com/zyprexadocs.html, http://www.furiousseasons.com/zip/seroqueldocs.zip, www.healthyskepticism.org/documents/Antipsychotics.php). However, having read through hundreds of such documents the authors found little to contradict and much to support the conclusions proffered here.

Acknowledgements The authors wish to acknowledge the work of journalist, Philip Dawdy, who has written much on these documents and whose website www.furiousseasons.com is one of the main hosts of internal industry documents. We also recognize the work of journalist Jim Edwards (http://industry.bnet.com/pharma/blog), who has written much about several of the documents discussed in this paper.

Disclosures Glen I. Spielmans has holdings of less than $10,000 in a mutual fund (Vanguard Health Care), which invests nearly exclusively in pharmaceutical companies. Dr. Parry is a member of Healthy Skepticism.

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Appendix A12:
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Correspondence

Commercial and non-commercial 'championing' of medications

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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' [1]. Mahli, Adams and Berk describe ways in which sponsored clinical trials can bias against lithium in favour of sponsored medications [2]. Mahli and Gershon note that 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].

Beyond these articles' excellent review of the role of lithium in pharmacotherapy, they raise the wider issue of trust in the pharmacotherapy evidence base in the medical literature. This has become a highly contentious topic in recent years [3,4]. For example Turner *et al.* found that for 74 Food and drug administration (FDA) registered studies of 12 antidepressants, publication and other bias led the medical literature to present 48 of the 51 (94%) published trials as positive for the antidepressants in question, whilst the FDA analysis including unpublished trials and accounting for other bias concluded only 38 of the 74 (51%) trials were positive [5].

Internal industry documents have come to light in litigation against the pharmaceutical industry that reveal the extent to which industry champions newly patented drugs in the medical literature, CME and advertising. This is unsurprising from a commercial perspective. In psychiatry the atypical antipsychotics as a class currently have longest patent life. From a commercial perspective they are medications in search of illnesses. 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'. For example, internal documents from Eli-Lilly in 1997 concerning its antipsychotic olanzapine (Zyprexa), included a slide entitled 'Bipolar vision of product evolution' that stated: 'To be a leader in the bipolar market, Zyprexa will need to be viewed as a *true mood stabilizer*' (italics in the original) and described needing to have efficacy in mania, depression and maintenance phases as well as off-label promotion for sub-syndromal 'complicated mood'. This was despite the documents also indicating the company did not have the data to support this aim [6].

It is thus vital for a trustworthy medical literature that there be transparency and greater separation of medication trials, journals and Continuing Medical Education (CME) from industry sponsorship. Medications need to be 'championed' on a true evidence base, not on marketing based information. In the meantime commercial realities mean that the medical profession itself will have to strive hard to champion off-patent medications that warrant a reminder to prescribers. Therefore thanks are due to Mahli *et al.* for championing an old, off-patent, yet beneficial medication.

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IACAPAP • BEIJING 2010
An Australian Perspective

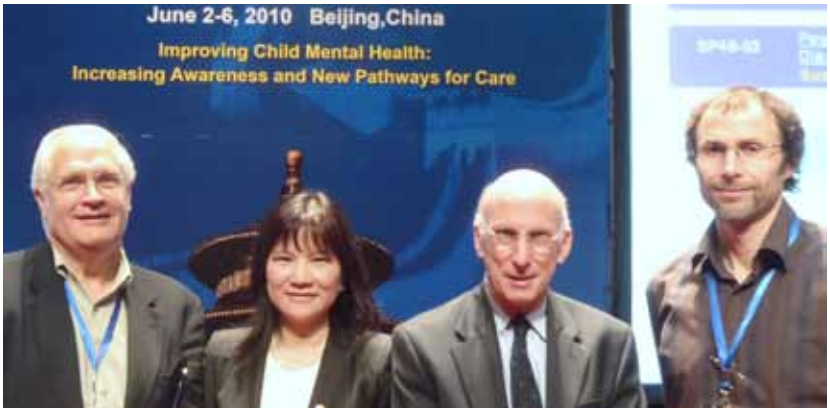
Everything about Beijing is big. The airport is vast (and I only saw terminal 3), the expanding clover leaves of highways flooded with 4 million brand new cars, the smog and haze that seemed even in the plane to stretch to the stratosphere, and the CNCC – the Chinese National Conference Centre – situated near the 'bird's nest' Olympic stadium. Following what seemed a mini version of the 'long march' through underground passages from the conference hotel, I arrived in the CNCC to walk past two engineering conferences and cavernous vacant halls that could have housed several more, finally seeing in the distance some people on an upper level – IACAPAP and over 1,000 delegates at the welcome reception were hidden up there. I had missed the opening ceremony and was even more disappointed when Ian Munt (Australia) informed me it had rivaled the opening ceremony of the recent Olympic Games.

Despite seeming small in comparison to the size of the building, the IACAPAP congress was far from small. There were 164 posters, 352 individual oral presentations, a further 211 oral presentations housed within 56 symposia, yet more in 23 workshops and courses, 21 state-of-the-art lectures and 9 keynote addresses. In addition, there were 4 industry-sponsored satellite symposia. All continents seemed well represented, particularly Asia, reflecting the increasingly strong development of child and adolescent mental health services in the emerging economic centre of our world. So it could all be rather overwhelming and thus I am very grateful to some of the Australian contingent (Ian Munt, Phil Hazell and Barry Nurcombe) for their assistance with this report.

"Professor Kang-E Michael Hong, of Seoul National University, delivered a state-of-the-art lecture on the importance of traditional culture to current East Asian society. China, Korea, Taiwan and Japan have undergone very rapid change associated with transition from a rural to an industrial economy. As a result, traditional concepts of living have been replaced by Western concepts of achievement, individuality, and self-realization. In fact, in China, during the time of Mao Tse Dong, Confucianism was banned. All these countries have seen the emergence of new social problems such as bullying, suicide, and 'hikikomori'. Professor Hong spoke of the need for a renascence of the traditional values of filial piety and family solidarity. He traced the history of Confucian thought and the influence of Lao Tse and Taoism. He argued for an amalgamation of traditional concepts and Western individualism, with the aim of leavening the dislocation caused by rapid social change," commented Barry Nurcombe, who chaired the session.

The opening keynote lecture was from Per-Anders Rydelius (Sweden), president of IACAPAP, on "Child and adolescent psychiatry - current status and developmental challenges." He highlighted the nature versus nurture debate, and illustrated the interaction between genetic predisposition and environment via the developmental histories of four cousins, all offspring of members of his own department. Later in the conference Andres Martin (USA), editor of the 'orange journal', gave a tantalizing preview of research in genetics and epigenetics to be published later this year.

Another keynote was delivered by David Schonfeld (USA) on "The impact of disasters on children." The individual impact of disaster such as the loss of family members and home affect children more than institutional or national aspects. Children who lost parents to motor vehicle accidents on the day of 9/11 were just as impacted as those whose parents died in the World Trade Centre. Schools and children's participation in memorializing peers, play a vital role in healing. Daniel Fung (Singapore), president of ASCAPAP, spoke on "Learning disorders: Aetiology, neuropsychology, assessment and intervention" and commented on a surprisingly strong correlation with westernized junk food diets and delinquency.



From left: Gordon Harper (USA), Susan Shur-Fen Gau (Taiwan), Myron Belfer (USA), and Peter Parry

Yi Zheng (China), president of the Chinese Child and Adolescent Psychiatry Society and president-elect of ASCAPAP, spoke on "China's 'one child policy' and child and adolescent mental health". The policy was introduced in the '70s in response to a near doubling of the population after the establishment of the People's Republic. Exemptions apply to ethnic minorities and rural Chinese, and those with a child with a disability. Parents who are only children may have more than one child at least 4 years apart. 400 million births have been prevented and the Chinese population is set to stabilize at 1.6 billion. Selective abortion and infanticide of female children is a serious issue and a public education program promotes the equal value of female children. Concern exists for the capacity to care for an aging population.

A session on complementary medicine and autism highlighted the fact this was China and a meeting of east and west as Virginia Wong (Hong Kong but trained in the UK), presented the remarkable results of a study using acupuncture for speech and language problems in children with quite severe autism.

As if to emphasize that globalization has many ills as well as benefits, John Howard (Australia) spoke on the serious levels of substance abuse being faced by the Pacific island nations. Drug smuggling into New Zealand and Australia has resulted in the Pacific nations now having an increased range of problems with substance abuse.

Laurence Greenhill (USA) gave an update on the "Controversy of child and adolescent psychopharmacology" featuring SSRIs' debatable risk/benefit ratio, metabolic side-effects of antipsychotics, and the risk of sudden cardiac death from stimulants. He considered the latter to be exceedingly rare and not warranting routine ECGs unless there is a family history of sudden cardiac death or cardiac conduction problems. On the contrary, Eric Taylor (UK) noted that approximately 10% of individuals on stimulant medication develop a rise in pulse rate and blood pressure. Although this is small, it is considered a risk factor in the long term and routine monitoring is indicated.

There were few presentations on pediatric bipolar disorder but Ellen Leibenluft (USA) showed that chronically irritable children who have been described by some researchers as 'broad phenotype pediatric bipolar disorder' are better characterized as 'severe mood dysregulation' based on lack of conversion to classical bipolar disorder in follow-up studies. Also differences in amygdala activity between the 'severe mood dysregulation' and so-called 'narrow phenotype pediatric bipolar disorder' cases have been found. Boris Birmaher (USA) had a similar message. It is in this context that the DSM-V task force is considering the already contentious new diagnosis of 'temper dysregulation disorder with dysphoria.'

Gordon Harper (USA) spoke of 'shifting paradigms' in North American child and adolescent psychiatry – from a biomedical and pharmacotherapy-focused paradigm towards a more holistic biopsychosocial and psychotherapeutic model – but also of continuing impediments within the US health system. In the same symposium, Susan Shur-fen Gau (Taiwan) reported on media and public antipathy towards the use of stimulant medication for ADHD in Taiwan, where teachers dispensing prescribed doses of methylphenidate had been pilloried in the media. In a sign of how the pendulum of opinion within cultures can swing, she noted a recent shift to some parents being eager for children to be on stimulants, even when not indicated.

ADHD was a frequent topic. Luis Rohde (Brazil), who is on the DSM-V ADHD task force, spoke of a likely loosening of criteria with the minimum age of onset being raised to 12 years and that this had already stirred controversy. There was also a meeting of the Asia Pacific ADHD Forum on the day prior to the IACAPAP congress, at which Phil Hazell (Australia) delivered a keynote address. Approaches to assessment and diagnosis are similar across Asia, although medication reimbursement varies. There is a strongly held clinical view that Asian children are more sensitive than European children to the anorectic effects of psychostimulant treatment. Separate work of Louis Rohde's group in Brazil is a large, well planned, prospective study of high school children at risk for psychosis, to elucidate how predictable the more common soft psychotic symptoms are towards later first episode psychosis.

There was not very much on attachment theory at the congress, apart from a keynote lecture by Charles Zeanah (USA) on "The importance of early experiences: Clinical, research and policy perspectives," which highlighted his group's research with orphans in Romania. They found a critical period of need for adoption — prior to age 2 — to allow near-full attachment recovery. However, in a session where I presented a critique of DSM-IV for being relatively "detached from attachment," Mingxin Zhan (China) presented a study with thorough methodology from Shanghai: "Family function and parental attachment of children with tic disorders." To my mind, it illustrated the sort of research needed for better understanding of how and to what extent attachment and developmental factors influence clinical presentations of DSM syndromes.

Olayinka Omigbodun (Nigeria), new president of IACAPAP

Many delegates took the opportunity to visit the Forbidden City, Great Wall and Beijing Opera. The conference gala dinner at the vast Summer Palace, preceded by boat rides on the large palace garden lake, was a highlight. Ian Munt likened the program in Beijing to a giant Chinese banquet menu, typified by the large program billboard in the foyer. He quipped: "after tasting the gastronomic delights of the Beijing 2010 IACAPAP congress I am certainly quite interested in taking a master class in French cuisine in Paris 2012."

Peter Parry

with the assistance of Ian Munt, Phil Hazell and Barry Nurcombe

Photos Scott Harding and others

Foreground, from left: Helmut Remschmidt, Andreas Warnke (both from Germany) and Barry Nurcombe

Adolescent Psychiatry, 2011, *1*, 61-66

Conflict of Interest as a Possible Factor in the Rise of Pediatric Bipolar Disorder

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In a formulation of an ethical guide for research developed by Columbia University (2003-2004), conflict of interest (COI) is defined as:

> A conflict of interest involves the abuse– actual, apparent, or potential – of the trust that people have in professionals. The simplest working definition states: A conflict of interest is a situation in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity.

This definition is applicable to work in the mental health field, including clinical practice, and not just medical research. We cite it here because it is both briefer and more focused than those offered at this time by our respective professional organizations. We also appreciate that it makes explicit the important issue of public trust.

The American Academy of Child and Adolescent Psychiatry's "code" of ethics (2009) laid out specific guidelines for its members. The codes dealing with third party influence (fidelity) include:

> Third-party influence may derive from many sources including guardians, health insurance providers, school system personnel, pharmaceutical companies, industry-related manufacturers, investment concerns, governmental agencies, and colleagues. The child and adolescent psychiatrist should not allow third parties, or the potential or actual compensation deriving from them, to improperly influence professional judgments and actions. These potential influences should not compromise the honesty, openness and transparency of clinical, educational, and research activities…. When possible conflicts of interest arise, the child and adolescent psychiatrist should fully describe the conflicts to all involved parties, and openly disclose these facts publicly when indicated.
>
> Attempts at third-party influence could include gifts, dinners, educational opportunities, recreational outings, medication samples, financial support, remuneration, and monetary investments. The child and adolescent psychiatrist should be conscious of these attempts at influence and how they might persuade the professional to act in ways that may be inconsistent with the best available scientific and clinical evidence and thus compromise the optimal provision of care. The child and adolescent psychiatrist should not accept enticements that compromise this Code's principles. When providing clinical care, teaching or engaging in promotional activities, the child and adolescent psychiatrist must declare third-party support from hospitals, insurance companies, pharmaceutical or other industries, and/or government grants, whether or not the professional perceives a conflict of interest.

These guidelines assist Child and Adolescent Psychiatrists (CAPs) in avoiding participating in or giving the appearance of participating in a COI. But the guidelines most relevant to this article are the ones which speak to the relationship between practitioners and the pharmaceutical industry. For many researchers, such relationships are difficult to avoid. Research funding from non-industry sources is limited. Also, in this era of relatively modest academic salaries, personal income from industry can be inviting. And the amounts of money that can flow from the pharmaceutical industry to researchers, as detailed below, can be substantial. It is reasonable to assume that, even given the best intentions of researchers, such income can unduly influence research.

There is evidence that supports the idea that unless COI guidelines are strictly adhered to, the financial power of the pharmaceutical industry can favor a particular theory that is industry's interests over alternative theories. One particular consequence that may have happened has to do with the reformulation of pediatric bipolar disorder (PBD), which was followed in time with an explosion in the frequency with which the illness has been diagnosed. This is a very discomforting article to write, but our concerns stem from

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2210-6766/11 $58.00+.00

awareness of the harms suffered by children who have been misdiagnosed and heavily medicated.

At a general level, supportive evidence for concern about COI comes from a number of books and articles, for example:

> *Truth About the Drug Companies: How They Deceive Us and What to Do About It.* By Marcia Angell (2005), Senior Lecturer in Social Medicine, Harvard Medical School. Angell draws upon her experiences as the former editor of the New England Journal of Medicine.
>
> *Our Daily Meds: How the Pharmaceutical Companies Transformed Themselves into Slick Marketing Machines and Hooked the Nation on Prescription Drugs*. By Melody Petersen (2008), a former reporter for the New York Times assigned to covering the pharmaceutical industry.
>
> *Shyness: How Normal Behavior Became a Sickness*. By Christopher Lane (2007). The author elaborates on a marketing device known as "disease mongering," in which a normal human attribute becomes pathologized and thus something for which a medication should be prescribed.
>
> *Medical Journals are an Extension of the Marketing Arm of Pharmaceutical Companies*. An article in PLoS Medicine by Richard Smith (2005) who was an editor at the British Medical Journal for 25 years, the last 13 of those as Editor-in-chief.

For more specific evidence to support our premise we turn to the work of investigators for the New York Times (NYT), the Wall Street Journal and those who worked for Senator Charles Grassley, Republican U.S. Senator from Iowa, whose sub-committee studied the influence of the pharmaceutical industry on the medical profession. Their work has been aided by that of attorneys using the courts to obtain corporate documents that reveal that marketing goals often take precedence over medical and scientific ethics.

Much of the investigative focus has been on certain "key opinion leaders," or KOLs, as they are known within the pharmaceutical industry. The Pharma Marketing Glossary defines KOLs as "physicians who influence their peers' medical practice, including but not limited to prescribing behavior," adding, "pharmaceutical companies generally engage key opinion leaders early in the drug development process to provide advocacy activity and key marketing feedback" (Pharma Marketing Network, 2003)

In a recent article in *Psychiatric Times,* Allen Frances (2010), who was chair of the DSM-IV task force, in describing factors that have led to what he termed the "fad" and "false epidemic" of PBD, attributed some of the cause to "prophets who were 'thought leading' researchers who encouraged child psychiatrists to ignore the standard bipolar criteria and instead to make the diagnosis in a free-form, over-inclusive way." He added, "Then enter the pharmaceutical industry – not very good at discovering new drugs, but extremely adept at finding new markets for existing ones."

Supporting Frances' opinion is the fact that several U.S. CAPs who are lead researchers in PBD have been prominent amongst medical practitioners cited for conflict of interests by Senate investigators and reporters.

How the KOL system can be influenced is discussed in a series of *New York Times* investigative reporting articles (Harris 2008; 2009; Harris & Carey, 2008) that alleged that a research psychiatrist from Massachusetts General Hospital, a Harvard affiliate, failed to disclose payments received from drug companies, and actually pushed one of the companies to fund a project implying that there would be a *quid pro quo*. Excerpting from one of the articles:

> …e-mail messages and internal documents from Johnson & Johnson made public in a court filing reveal that Dr. Biederman pushed the company to finance a research center at Massachusetts General Hospital, in Boston, *with a goal to "move forward the commercial goals of J.& J.*" (italics added).

The reporter also maintained that the documents also showed that the company prepared a draft summary of a study that Biederman was said to have written. (Harris, 2008).

It seems likely to us that Biederman's work helped to fuel a fortyfold increase from 1994 to 2003 in the diagnosis of pediatric bipolar disorder and a rapid rise in the use of powerful, risky and expensive antipsychotic medicines in children. Dr. Biederman has had a vast influence on the field. Undoubtedly this influence is in part due to his position at one of the most prestigious medical institutions. Industry documents such as emails concerning Dr Biederman being "a very powerful national figure in child psych" (Goldberg, 2008) and favorably commenting on "the utility of partnering with a group such as MGH, who has the potential of reaching and having a significant impact upon the field of child and adolescent psychiatry" (Sharav, 2002) reveal that such influence is highly valued pharmaceutical industry research sponsors.

In June 2008, a Congressional investigation led by Senator Grassley, reported information they obtained from conflict of interest forms from Harvard University, as well as information from drug companies about what they paid doctors. The senator reported to Congress that this material revealed that Dr. Biederman had failed to report to Harvard at least $1.4 million in outside income from Johnson & Johnson and other makers of antipsychotic medicines. In one example given by Senator Grassley, Dr. Biederman reported no income from Johnson & Johnson for 2001 in a disclosure report filed with the university. According to Senator Grassley, when asked to check again, Dr. Biederman said he had received $3,500. But Mr. Grassley said Johnson Johnson told him that it paid $58,169 to Dr. Biederman in 2001.

Reporting on documents made public as a result of a court filing, New York Times reporter Harris (2008) quoted a February 2002 e-mail message from Georges Gharabawi, a Johnson & Johnson executive, which said Dr. Biederman approached the company "multiple times to propose the creation" of the center and Gharabawi further stated that "the rationale of this center is to generate and disseminate data supporting the use of risperidone in this patient population" (Gharabawi, 2002). The documents from Johnson and Johnson reportedly showed that the Company gave the center $700,000 in 2002 alone.

Personal income from industry can be substantial: According to Senator Grassley (2008): "[Drs. Biederman, Spencer and Wilens]…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." The Senator goes on to report that after initially denying it, "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…."

Harris reports in the NYT (2009) that, "…Drs. Joseph Biederman, Thomas Spencer and Timothy E. Wilens—are named in the subpoena, which was sent … [to] a lawyer who represents state attorneys general in lawsuits that claim makers of antipsychotic drugs defrauded state Medicaid programs by improperly marketing their medicines."

Continuing to critique the problems with COI and PBD research, Harris and Carey (2008) comment:

> Many researchers strongly disagree over what bipolar looks like in youngsters, and some now fear the definition has been expanded unnecessarily, due in part to the Harvard group.
>
> Controlling for bias is especially important in such work, given that the scale *(the Young Mania Rating Scale)* is subjective, and raters often depend on reports from parents and children, several top psychiatrists said.
>
> More broadly, they said, revelations of undisclosed payments from drug makers to leading researchers are especially damaging for psychiatry.
>
> "The price we pay for these kinds of revelations is credibility, and we just can't afford to lose any more of that in this field," said Dr. E. Fuller Torrey, executive director of the Stanley Medical Research Institute, which finances psychiatric studies. "In the area of child psychiatry in particular, we know much less than we should, and we desperately need research that is not influenced by industry money."

Torrey is a researcher and advocate, who has long argued that pharmaceutical companies have too much influence over psychiatric organizations and psychiatrists, effectively buying them off (Torrey, 2002). Another CAP KOL in PBD research was also investigated by the Grassley committee. Another New York Times article (Rubenstein, 2008) quotes the Senator as saying:

> "Today, I am going to report on the actions of one physician to explain how industry payments to medical experts can affect medical practice," Grassley said by way of introducing his remarks. Grassley then reviewed the funding for Melissa DelBello, who had reported to the University of Cincinnati that she had received $100,000 from AstraZeneca in 2003, the year after the study's publication in the *Journal of the American Academy of Child and Adolescent Psychiatry*. She reported another $80,000 in 2004. The payments covered lectures, consulting fees, service on advisory boards and reimbursements for travel-related costs, Grassley said (2008).
>
> DelBello, who also has received NIH grants, also reported $100,000 in outside income between 2005 and 2007. But when Grassley asked AstraZeneca directly, the total value of its payments to DelBello during those three years came to $238,000. "The fact that a physician can promote a drug to other doctors and receive NIH funding, while hiding a very clear conflict of interest, is disturbing," Grassley concluded (2008).

The researchers cited may of course have good explanations and Biederman put forward his case in a letter to the Wall Street Journal (2008). Nonetheless these allegations of COI have significant potential to erode public trust and diminish the reputation of child psychiatry. There has been much concern about research bias in the medical literature of late (McGauran, Wieseler, Kreis, Schüler, Kölsch, & Kaiser, 2010). Spielmans and Parry (2010) also suggest that the current ideal of "evidence-based medicine" is in reality frequently usurped by "marketing-based medicine." Marketing goals drive the types of trials industry funds and, as drug trial sponsors, industry sees raw data as their own commercial property, not the property of principal researchers. Internal documents released through litigation from Eli-Lilly (1999) concerning olanzapine indicate the company saw promoting olanzapine as a "mood-stabilizer" along with a growth in diagnoses of bipolar disorder as important to financial success. A document regarding expanding indications for olanzapine while targeting primary care physicians, included jottings saying: "…must have bipolar indication to explode…create a market". (Eli-Lilly, 1999).

This information raises questions, even if the state of our knowledge about PBD were far more advanced than it is. For many years there was little or no perception of bipolar disorder occurring in children, leading Carlson, one of the early researchers in this field, to wonder if prepubertal cases of mania were being overlooked (1984). Twenty five years later, she indicated that while she was clear they did occur, she now considered them to be over diagnosed (Carlson,

Potegal, Argulies, Gutkovich, & Basile, 2009). Nonetheless, an explosion in diagnoses of bipolar disorder in youth occurred from 1994-95 to 2002-03, with the number having increased 4,000%, with a still rising trajectory (Moreno, Gonzalo, Blanco, Jiang, Schmidt, & Olfson 2007). This steep rise in the number of reported PBD cases occurred after the publication of an article by Wozniak, Biederman, and other colleagues at Massachusetts General Hospital (1995) that advocated revised diagnostic criteria for PBD. The authors re-characterized the disorder so that mood was less relevant. The new defining characteristic was now said to be anger and irritability, and 98% of their reported cases had comorbid ADHD.

As anger, irritability, limited concentration and hyperactivity can be very much a part of normal childhood and also frequently present as non-specific symptoms in a wide variety of disorders, the new criteria made matters more confusing for parents, children and clinicians.

It is clear that many parents and schools struggle with children presenting with affect dysregulation and associated behavioral problems. We believe one can differentiate bipolar disorder, when it is in fact there, from other reasons for a child's behavior. But it is a difficult task, as Jennifer Harris has pointed out (this issue). We believe that an appropriate understanding of a child's complex and potentially troubling actions requires a thoughtful and time consuming evaluation. The principal players (parents, the child, pediatricians, teachers, previous evaluators and therapists) all need be involved. Records must be reviewed, and an open mind and much listening are required. It is essential to explore all one can about a child, his family and culture in the most non-threatening ways possible. A potential hazard is that, if one approaches such evaluations with an over commitment to finding a singular explanation—say, either this child's behavior is entirely due to a chemical imbalance, or for that matter, to a narrow psychoanalytic explanation—a diagnostic error may likely result.

An over focus on a chemical imbalance carries the seductive proposition that a rapid and easy fix can be obtained with hoped for magic pills and other contextual issues may be overlooked. Parents may feel it is less stigmatizing to have a child with an inherited biologic disorder, as opposed to the parents perhaps being in need of parental guidance, child counseling or, even less appealing, the recommendation of their own psychotherapy. And, understandably, many therapists, especially those working in public agencies which are understaffed and over populated with angry youth, find it troubling to listen to tales of neglect, trauma, educational and societal disadvantage, poverty and racism. It can be incredibly difficult to listen to these things for a variety of reasons. The more intimate, personal ones are painful to hear. The ones that have to do with larger societal problems, about which an individual clinician acting alone can do little, can lead to despondency and nihilism about the possibility of change.

Further, there can be material rewards for making a biologic diagnosis. In the current U.S. health system, the psychiatrist's work as a provider of medication is almost always better reimbursed by insurance than is the providing of individual or family psychotherapy. In addition, a variety of services, such as hospitalization, special education, classroom accommodations, and respite care, are usually more readily available to families when the child is given a label with biologic implications. This can lead to "diagnostic upcoding," which refers to the therapist, consciously or not, inflating the diagnosis in an effort to procure more care for the patient and family and perhaps more income for him or herself. It is noteworthy that in Europe and Australia where CAPs are more equitably remunerated for providing non-pharmacological therapies, the diagnosis of PBD is far less common than in the USA.

Despite these forces favoring the use of a narrow biologic reductionistic approach, there are indications that the pendulum is beginning to swing back away from the excessively biologic position of the past two decades. It is likely that a variety of occurences are responsible for this. One important element certainly is negative media attention, such as reported above, which has raised the consciousness of both professionals and the lay public about COI.

In addition, reforms in recent years have encouraged compliance with the ethical guidelines such as those of the AACAP presented above. A number of hospitals and academic institutions have banned easy drug company access to staff and trainees, along with the associated free meals and gifts. Some Continuing Medical Education (CME) programs have dispensed with pharmaceutical funding. Both providers of CME programs and editors of medical journals appear more conscientious in requiring COI declarations. The FDA has in recent times appeared to exercise its regulatory responsibilities more stringently.

It remains to be seen to what extent the health reforms pushed by the Obama administration will lead to improved care, but here again is some room for hope. Were meaningful improvements to take place, these might well include mental health reimbursement policies that put individual and family psychotherapy on a more even footing with the prescribing of medications.

If the continuing education and journal reforms become progressively stronger, mental health practitioners in general and psychiatrists in particular may be less resistant to doing the hard work, which so often involves overcoming considerable discomfort in order to fully listen and understand the narratives of our patients. They would then become more resistant to seeking or providing magic pills, whose side-effects too often outweigh their less than magical benefits. And CME programs focused on alternatives to pharmacotherapy might then become more the norm.

Recent actions on the part of the leadership of two large U.S. psychiatric organizations, speak to positive change. In 2007 the American Psychiatric Association began to reduce all industry-sponsored symposia at its annual meeting, with a goal of eliminating such symposia entirely in 2011 (Cassels, 2010b). It is noteworthy that undertaking this measure had a considerable economic impact on the organization, forcing it to cut staff and components; Jay Scully, the APA's Medical Director, estimated that the cost in lost revenue in 2009 was

$2 million, or about 3.3% of the APA's total annual budget (*ibid.*).

However, the APA's leadership in the area of COI has not been unambivalently embraced by its membership (at least insofar as its Assembly's actions reflect their views). At its May 2010 meeting, the Assembly refused to vote on a document on COI by a workgroup headed by Paul Appelbaum, a former APA President. What became known as the "Appelbaum Report" advocated strict limits on acceptance of gifts from pharmaceutical companies and recommended that psychiatrists not serve on speakers bureaus or take any form of remuneration from drug companies. It was introduced for consideration of the APA Assembly. (The full report may be read online at <www.psych.org/Departments/GOV/Assembly-On-line-Packet – May-2010/Assembly-Packet.aspx> by clicking on "Section 13.")**)** Dr. Louise Mullan (2010), a Member in Training of the American Psychiatric Association (APA) wrote about this in *Psychiatric News*, an official publication of the APA. She protests the fact that the assembly referred the issue to committee where it died, writing, "…[the] May Assembly meeting (of the APA) was our chance to have an open, plenary-session debate and to pull together to establish a clear, comprehensive, living document that would provide our profession with ethical guidance in an increasingly important area." She further states:

> If one looks at other professional bodies, it appears that we in psychiatry are behind the times when it comes to reining in potential conflicts of interest. In a profession focused on patient's psychological needs, we have failed to show those patients that we value their need for clarity more than we do the possible benefits we would derive from our ties with industry. We lag behind organizations like the Association of American Medical Colleges, Council of Medical Specialty Societies, and Institute of Medicine, which have drawn up clear sets of guidelines as extensive in scope as those proposed in the Appelbaum report (on ethical guidelines). *(The authors note here that in 2009 the AACAP did incorporate the Applebaum report in its ethical guidelines.)*

We find it encouraging both that Dr. Mullan had the courage to make public her criticism of the APA and that the APA allowed her the use of its newspaper in which to do it. Colleagues have noted that the issue spans a generational divide, with older members who are used to close relationships with pharmaceutical companies tending to fail to fully appreciate COIs, while younger members tend to advocate for change (Cassels, 2010a).

The second positive development concerns Lawrence Greenhill (2010), the President of the American Academy of Child and Adolescent Psychiatry (AACAP). An email he sent to the members of the AACAAP announced: "The *New York Times* today (9.2.2010) published an article, *'Child's Ordeal Shows Risk of Psychosis Drugs for Young.'* It features four Academy members and a quote from me, Larry Greenhill, M.D., AACAP President."

The message had a link to the article, which detailed the very negative effects on a child who was over diagnosed and over medicated from age 18 months to 3 years of age and his gradual recovery once the drugs were discontinued (Wilson, 2010). Dr. Greenhill is quoted as saying, "Psychotherapy is the key to the treatment of preschool children with severe mental disorders, and antipsychotics are adjunctive therapy—not the other way around."

These refreshing statements have been a long time in coming. They have made us feel encouraged, proud and hopeful.

DISCLOSURES

Neither author has pharmaceutical industry or other financial disclosures to make. Dr. Parry is a member of the organization Healthy Scepticism (www.healthyscepticism.org), an international organization of physicians, pharmacists and other health professionals that monitors Pharma-Medicine matters.

ADDENDUM

Since the writing of the above article, it has come to our attention that the Conflicts of Interest Work Group, Fall, 2010, established by the APA Assembly, has developed an Action Paper which sets forth extensive guidelines for managing conflicts of interest. The Action Paper is now to be sent to the APA Board of Trustees so that the guidelines might be adopted as APA policy.

The principles and guidelines, derived from the *Institute of Medicine report: Conflicts of Interest in Medical Research, Education And Practice*, [Bernard Lo and Marilyn Field, Editors (2009), ISBN: 978-0-309-13188-9, Website (summary) www.nap.edu/catalog/12598.html], were developed for special relevance to clinical practice and research. They encourage, "members (to) exercise vigilance, caution, and strive for the prevention of conflict whenever possible." Members are cautioned about accepting gifts, meals and marketing information from pharmaceutical representatives. The guidelines specifically state, "Conflict of interest ethical principles and ongoing studies should be integrated parts of continuing medical education, including distinguishing marketing and promotion from balanced, scientific clinical evidence." and, "...funding (of research and education) should be commensurate to the research and reflect active participation and documented remuneration."

While it remains for the APA Board to accept these recommendations, we identify the work of the COI Work Group as a further encouraging sign of progress for psychiatry.

By: Edmund Levin and Peter Parry, November 2010.

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Aripiprazole in the Maintenance Treatment of Bipolar Disorder: A Critical Review of the Evidence and Its Dissemination into the Scientific Literature

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Abstract

Background: Aripiprazole, a second-generation antipsychotic medication, has been increasingly used in the maintenance treatment of bipolar disorder and received approval from the U.S. Food and Drug Administration for this indication in 2005. Given its widespread use, we sought to critically review the evidence supporting the use of aripiprazole in the maintenance treatment of bipolar disorder and examine how that evidence has been disseminated in the scientific literature.

Methods and Findings: We systematically searched multiple databases to identify double-blind, randomized controlled trials of aripiprazole for the maintenance treatment of bipolar disorder while excluding other types of studies, such as open-label, acute, and adjunctive studies. We then used a citation search to identify articles that cited these trials and rated the quality of their citations. Our evidence search protocol identified only two publications, both describing the results of a single trial conducted by Keck et al., which met criteria for inclusion in this review. We describe four issues that limit the interpretation of that trial as supporting the use of aripiprazole for bipolar maintenance: (1) insufficient duration to demonstrate maintenance efficacy; (2) limited generalizability due to its enriched sample; (3) possible conflation of iatrogenic adverse effects of abrupt medication discontinuation with beneficial effects of treatment; and (4) a low overall completion rate. Our citation search protocol yielded 80 publications that cited the Keck et al. trial in discussing the use of aripiprazole for bipolar maintenance. Of these, only 24 (30%) mentioned adverse events reported and four (5%) mentioned study limitations.

Conclusions: A single trial by Keck et al. represents the entirety of the literature on the use of aripiprazole for the maintenance treatment of bipolar disorder. Although careful review identifies four critical limitations to the trial's interpretation and overall utility, the trial has been uncritically cited in the subsequent scientific literature.

Please see later in the article for the Editors' Summary.

Citation: Tsai AC, Rosenlicht NZ, Jureidini JN, Parry PI, Spielmans GI, et al. (2011) Aripiprazole in the Maintenance Treatment of Bipolar Disorder: A Critical Review of the Evidence and Its Dissemination into the Scientific Literature. PLoS Med 8(5): e1000434. doi:10.1371/journal.pmed.1000434

Academic Editor: Phillipa J. Hay, University of Western Sydney, Australia

Received August 3, 2010; **Accepted** March 23, 2011; **Published** May 3, 2011

Funding: The authors received no specific funding for this study. ACT received salary support as a Robert Wood Johnson Health and Society Scholar at Harvard University. No funding bodies had any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: ACT receives salary support through the Robert Wood Johnson Foundation Health and Society Scholars Program. The Robert Wood Johnson Foundation's stated mission is to improve the health and health care of all Americans. NZR is a member of the National Physicians Alliance, a not-for-profit organisation whose stated primary goal is to restore physicians' primary emphasis on the core values of service, integrity, and advocacy. The National Physicians Alliance rejects funding from commercial health care interests and encourages its members to do the same. NZR, JNJ, and PIP are members of Healthy Skepticism, an international not-for-profit organisation whose stated aim is to improve health by reducing harm from misleading drug promotion; GIS joined Healthy Skepticism after this article was accepted for publication. GIS is a current shareholder (<$10,000) in a mutual fund, Vanguard Healthcare, that invests heavily in pharmaceutical companies. DH reports no links to pharmaceutical companies in the past 5 years. ACT is a former board member of the ethics committee, and former member, of the National Physicians Alliance. ACT and NZR are former members of No Free Lunch, a not-for-profit organisation whose stated mission was to encourage health care providers to practice medicine on the basis of scientific evidence rather than on the basis of pharmaceutical promotion. JNJ was engaged by the law firm of Baum, Hedlund, Aristei & Goldman to provide an independent analysis of the data in Glaxo SmithKline's Study 329 of paroxetine in adolescents. DH has been an expert witness in ten legal cases involving antidepressant medications and one case involving the patent on olanzapine (Zyprexa).

Abbreviations: CI, confidence interval; NDA, new drug application.

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Introduction

First-generation antipsychotic medications have been used for many decades in the short-term treatment of acute manic episodes associated with bipolar disorder [1]. Second-generation antipsychotic medications have increasingly gained popularity for this use as well [2]. However, their promotion for the maintenance treatment of bipolar disorder is a more recent phenomenon [3–6]. In one recently published nationally representative survey of physicians, mood disorders accounted for the majority of antipsychotic medication prescriptions [7], and a recent shift to prescription of antipsychotic medications was observed in a sample of San Diego county Medicaid beneficiaries with bipolar disorder [8].

Traditionally, the clinical care of patients diagnosed with bipolar disorder has been divided into three phases (borrowed from clinical consensus about the phases of treatment for major depressive disorder [9,10]): treatment of acute episodes to symptomatic remission, continuation treatment to prevent relapse, and maintenance treatment to prevent recurrence. The 2 mo following recovery from the acute episode is commonly described as acute phase recovery, and the continuation phase of treatment (during which the natural course of the episode is considered still active even though the patient may be asymptomatic) is defined as lasting from months 2 through 6 [11,12]. The medication used for treatment in the acute phase is often extended for treatment in the continuation and maintenance phases [13,14] and in this context may include lithium, valproate, lamotrigine, or a second-generation antipsychotic medication such as olanzapine, aripiprazole, quetiapine, risperidone, or ziprasidone [15]. However, although the use of second-generation antipsychotic medications to treat acute mania is supported by a relatively well-established evidence base [16–18], efficacy in treatment of acute mania does not necessarily imply efficacy for maintenance or prophylaxis [13,19,20]. As Goodwin and Jamison note: "Simply because a drug has anti-manic properties (and if continued, will protect against relapse back into mania in the months after the acute episode), one cannot assume that it will be effective in the prevention of new episodes. While this assumption may be true (to some extent) for lithium, it is not well supported by the data with respect to all the other antimanic agents" (p. 800) [21].

Despite the need for robust evidence on the maintenance and/or long-term prophylactic treatment of bipolar disorder, to date very little has been supplied in this regard [4,15,22,23]. There remains little consensus about recommended courses of maintenance or prophylactic treatment, and consequently overall psychopharmacological treatment patterns vary widely [24–28]. Aripiprazole, first approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia in 2002, is the newest of the second-generation antipsychotic medications to have obtained FDA approval for use in bipolar disorder. In 2004 it was approved for the treatment of acute manic and mixed episodes associated with bipolar disorder, and in 2005 it was granted an additional indication for the maintenance treatment of bipolar disorder [29]. Since its approval, aripiprazole has rapidly become a popular choice among clinicians in the maintenance treatment of bipolar disorder. Total U.S. sales for aripiprazole (across all indications) increased from US$1.5 billion in 2005 to US$4 billion in 2009 [30]. In a recent study in which U.S.-based physicians were queried about their preferred pharmacological treatments for schizophrenia and bipolar disorder, only 3% of psychiatrists and 7% of primary care physicians named aripiprazole as their first choice for treating schizophrenia, whereas 23% of psychiatrists and 16% of primary care physicians named aripiprazole as their first choice for treating bipolar disorder [31]. Consistent with this survey, from 2002–2007, the most common indication for the prescription of aripiprazole in office-based practice settings was for bipolar disorder (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] Diagnosis Code 296.0) [32].

In the setting of chronic illnesses such as bipolar disorder, critical appraisal of long-term treatments has important implications for policy making. Overall medication costs for the chronically ill are driven largely by decisions about the ongoing use of prescription medications, rather than by decisions about whether to initiate their use [33]. Spending on prescription medications is the fastest-growing category of the U.S. health care budget [34], further underscoring the need for a rigorous evidence-based approach regarding their prescription and use. Given the rapid adoption and widespread use of aripiprazole in the maintenance treatment of bipolar disorder, we decided to review the scientific data supporting its use in this setting. A secondary aim of this study was to examine the diffusion of this data into the subsequent scientific literature.

Methods

Primary Evidence Search

We sought to identify double-blind (i.e., where participants and physicians administering medications were blind to treatment assignment), randomized controlled studies of aripiprazole for the maintenance treatment of bipolar disorder, while also avoiding inadvertent inclusion of acute treatment studies or other study designs. Therefore we required studies to have a duration greater than 4 mo in order to be included in our review, and excluded open-label, acute, and adjunctive studies. We searched for published literature as well as unpublished and ongoing clinical trials, with no language restrictions. The following systematic search strategy was employed to search PubMed: "bipolar disorder"[MeSH Terms] OR ("bipolar"[All Fields] AND "disorder"[All Fields]) OR ("bipolar disorder"[All Fields]) AND ("aripiprazole"[Substance Name] OR "aripiprazole"[All Fields]) AND ("maintenance"[MeSH Terms] OR "maintenance"[All Fields]). We also searched Scopus (including Embase and MEDLINE) using the same search terms ("bipolar disorder" OR "bipolar" AND "disorder" AND "aripiprazole" AND "maintenance"). We also searched ClincalTrials.gov, the Cochrane Central Register of Controlled Trials (Issue 3 of 4, July 2010), and the World Health Organization International Clinical Trials Registry Platform Search Portal using the terms "aripiprazole" and "bipolar." We did not attempt to contact the manufacturer directly to inquire about possibly unpublished trials, but we screened all listings on the Bristol-Myers Squibb Clinical Trials Disclosure Web site under Clinical Trial Results, Psychiatric Disorders [35]. All searches were conducted in July 2010. And finally, we submitted a request under the U.S. Freedom of Information Act [36] for the supplemental New Drug Application (NDA) filed by the study sponsor to obtain additional labeling for the use of aripiprazole as maintenance therapy in bipolar I disorder [29], and we searched it manually for further reference to other published or unpublished studies.

Citation Search

We also sought to better understand the influence of the primary evidence on the broader scientific literature. To do this, we used the Web of Science(R) Science Citation Index Expanded

to search for articles that cited the primary evidence identified through the evidence search protocol detailed above. Next, we evaluated the articles on how they cited the primary evidence, using criteria similar to those used in a previous study on the quality of news media reports of medication trials [37]. Each of the citing articles was rated on three quality criteria by a single study author (NZR). A 15% random sample of articles ($n = 15$) was double-coded independently by another study author (ACT), and the Cohen's kappa coefficient was calculated in order to assess the degree of inter-rater agreement [38]. We chose dichotomous quality ratings to provide conservative estimates of citation quality and in order to limit subjective judgments by the rater. First, articles were screened for any mention of the use of aripiprazole specifically for ongoing, maintenance, or prophylactic treatment of bipolar disorder. If the answer to this question was "yes," then the article was further rated on the three quality criteria: (1) whether the article reported any quantitative data from the primary evidence (e.g., odds ratios, percentages, or *p*-values); (2) whether the article mentioned any adverse events described in the primary evidence; and (3) whether the article mentioned any limitations of the primary evidence.

Although our citation search protocol was not specifically targeted towards identifying treatment guidelines and review articles on pharmacological treatment strategies in bipolar disorder, we manually highlighted for further discussion those that were identified in the citation search. Our citation search protocol likely underestimates the influence of the primary evidence because we did not also use a database such as Google Scholar that could have also identified guidelines implemented by hospitals, government, or other institutions whose documents in this area have not been published in peer-reviewed journals or indexed in services such as PubMed. However, we chose to highlight treatment guidelines and reviews because they can be particularly influential in shaping prescribing behavior.

Results

Our primary evidence search protocol identified 177 unique citations (Figure 1). Of these 177 citations, only two publications met criteria for inclusion in our review [39,40]. Searching the clinical trials registries yielded two listings meeting inclusion criteria, but these referred to the two publications already identified (Figure 2) [39,40]. Further details on the excluded acute and adjunctive studies are provided in Tables S1 and S2. Two unpublished trials initially appeared to meet criteria for inclusion but were ultimately excluded. The first, Otsuka NCT00606177 [41], was a 3-wk placebo-controlled trial of aripiprazole for treatment of acute mania with a 22-wk extension phase, but it was described as currently still recruiting study participants. The second, BMS CN138-135LT [42], was a completed 40-wk extension of a 12-wk randomized lithium- and placebo-controlled trial of aripiprazole for acute mania. Although the 12-wk acute outcomes data from BMS CN138-135 were published in a peer-reviewed journal [43], the outcomes data from the 40-wk extension have not, to our knowledge, been published (and the little data made available in the synopsis posted online by the

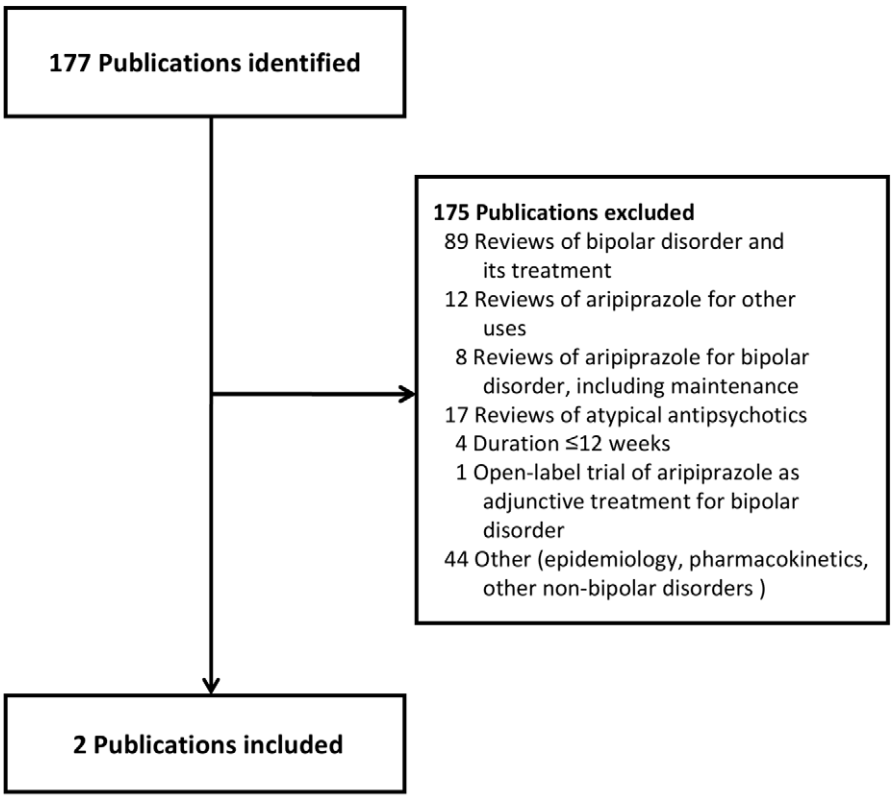

Figure 1. Publications identified for review. These publications were identified using a systematic search of PubMed and Scopus, as well as a manual search of the supplemental new drug application submitted to the FDA to obtain an additional indication for the use of aripiprazole in the maintenance treatment of bipolar disorder.
doi:10.1371/journal.pmed.1000434.g001

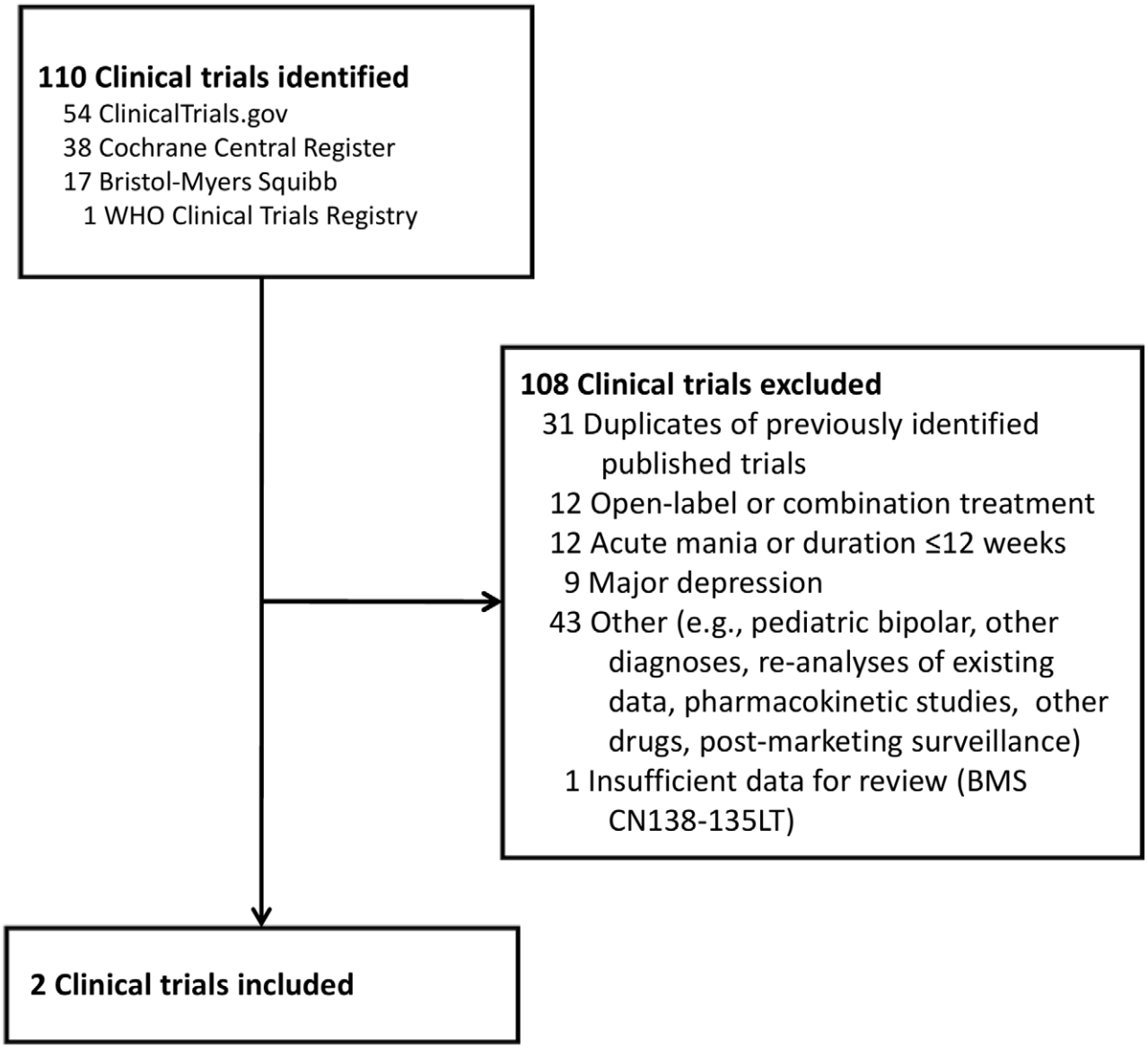

Figure 2. Clinical trials identified for review. These clinical trials were identified using a systematic search of ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, the World Health Organization (WHO) International Clinical Trials Registry, and the Bristol-Myers Squibb Clinical Trials Disclosure Web site, as well as a manual search of the supplemental new drug application submitted to the FDA to obtain an additional indication for the use of aripiprazole in the maintenance treatment of bipolar disorder. The "duplicates" were each matched to published studies (see Figure 1).
doi:10.1371/journal.pmed.1000434.g002

manufacturer were inadequate for detailed critical assessment). The manufacturer's synopsis indicates that 4.5% of participants on aripiprazole completed the extension phase, compared to 8.1% for those on lithium. A third arm of the study, completed by 8.5% of participants, entailed treatment with placebo for 3 wk followed by crossover to aripiprazole. Finally, the supplemental NDA contained no references to additional studies, published or unpublished, meeting inclusion criteria (Text S1) [29].

The two peer-reviewed publications included in our review report the results of a single randomized trial (hereafter referred to as "the Keck trial") implemented under the auspices of the Aripiprazole Study Group and sponsored by the manufacturer of the drug, Bristol-Myers Squibb Co. One publication describes the initial 26-wk double-blind phase [39], and the other its 74-wk extension [40]. We also identified a post hoc subgroup analysis of data from the Keck trial focused on participants diagnosed with the rapid-cycling variant of bipolar disorder [44]. We also identified a separate trial [45], also authored by Keck and colleagues, examining the efficacy of aripiprazole in the treatment of acute manic episodes, with outcomes assessed at 3 wk. Given the paucity of available evidence on aripiprazole for the maintenance treatment of bipolar disorder, we decided to review the Keck trial [39,40] in detail.

The Keck Trial

A total of 633 adult participants meeting DSM-IV criteria for bipolar I disorder were enrolled in the Keck trial. A flow chart of

the trial is shown in Figure 3. For inclusion, participants must either have completed a prior 3-wk acute mania trial [45], met eligibility criteria for a prior acute mania trial but declined participation in that trial, or experienced a manic or mixed episode within the prior 3 mo. The publication describing the 26-wk double-blind phase [39] indicates that participants were recruited from 76 sites in the U.S., Mexico, and Argentina (but does not specify the numbers of sites within each country or the numbers of patients from each site). Of the original enrollees, 567 entered the "stabilization phase," which consisted of open-label treatment with aripiprazole for 6–18 wk. Participants remained in this phase until their Young Mania Rating Scale (YMRS) was ≤ 10 and their Montgomery-Asberg Depression Rating Scale (MADRS) was ≤ 13 during four consecutive visits over a minimum of 6 wk. 206 participants completed the stabilization phase. Of these, 161 entered the double-blind phase. The supplemental NDA indicates that participants who completed the stabilization phase and entered randomization were derived from 45 sites in the U.S. ($n = 124$), three sites in Argentina ($n = 7$), and two sites in Mexico ($n = 30$). These 161 participants were assigned either to an intervention arm in which they continued taking aripiprazole at the stabilizing dose ($n = 77$ or 78; both numbers are reported [40]) or to a placebo arm in which aripiprazole was abruptly discontinued and replaced with placebo ($n = 83$). 39 (50% of the 77 or 78 who entered randomization) in the intervention arm and 28 participants (34%) in the placebo arm completed the 26-wk double-blind phase. Time to relapse was described as longer for participants treated with aripiprazole compared to those who were switched to placebo. Mean times to relapse were not provided, but the hazard ratio for relapse was given as 0.52 (95% confidence interval [CI] 0.30–0.91). When time to relapse was partitioned into manic versus depressive relapse, the difference in overall time to relapse was found to be driven primarily by an effect on manic relapse (23% relapse rate on placebo versus 8% relapse rate on aripiprazole). No differences in time to depressive relapse (13% versus 12%) or to mixed state relapse (6% versus 5%) were noted. Keck and colleagues concluded that aripiprazole "was superior to placebo in maintaining efficacy in patients with bipolar I disorder with a recent manic or mixed episode who were stabilized and maintained on aripiprazole treatment for 6 weeks" (p. 626) [39].

The extension phase of the Keck trial, published as a separate paper [40], followed the remaining participants over the subsequent 74 wk: 27 participants in the placebo group (of the 28 who completed the double-blind phase) and 39 participants in the aripiprazole group. The authors concluded: "Over a 100-week treatment period, aripiprazole monotherapy was effective for relapse prevention in patients who were initially stabilized on aripiprazole for 6 consecutive weeks, and it maintained a good safety and tolerability profile" (p. 1480) [40]. Similar to the data from the first 26 wk, time to manic relapse was reported to be longer for the aripiprazole group (with no difference between groups in time to depressive relapse).

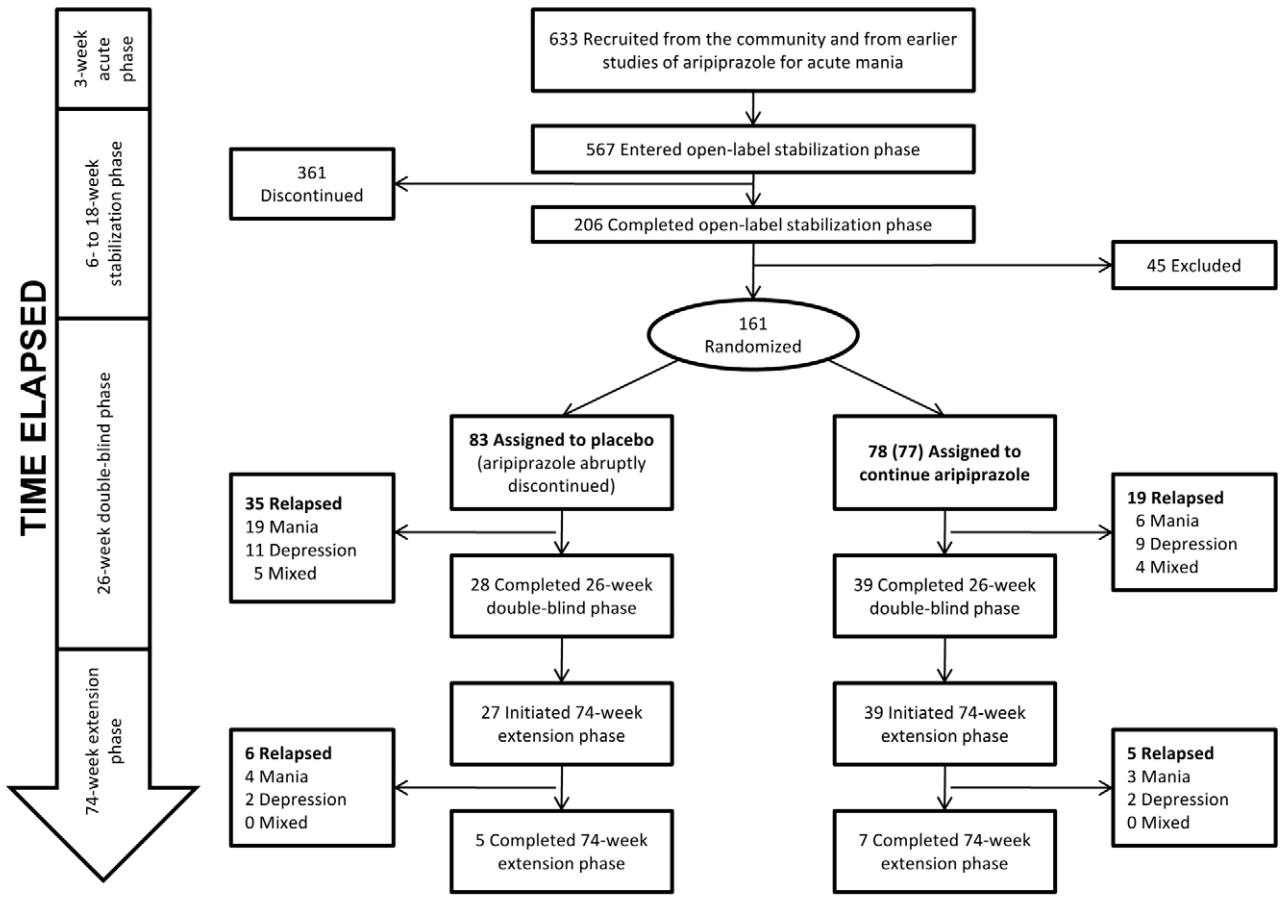

Figure 3. Keck study participant flow. Participants had to complete the 6- to 18-wk stabilization phase before they were eligible for randomization. After completion of the 26-wk double-blind phase, participants were invited to continue in the 74-wk extension phase.
doi:10.1371/journal.pmed.1000434.g003

Four Substantive Criticisms of the Keck Trial

Although the Keck trial was the sole basis for aripiprazole receiving an additional FDA-approved indication for the maintenance treatment of bipolar disorder [29], we believe that reading the Keck trial as supporting the use of aripiprazole for this indication is an overinterpretation of the trial's design and the data it generated. First, the duration of the Keck trial was insufficient to demonstrate prophylactic efficacy. Second, the double-blind phase of the Keck trial was based on an enriched sample of patients who had already responded to the medication during the stabilization phase, thereby limiting generalizability of the trial's findings. Third, the randomized discontinuation design of the Keck trial may conflate iatrogenic adverse effects of abrupt medication discontinuation with the beneficial effects of short-term continuation treatment. All of the putative benefit occurred during the double-blind phase of the trial, and little improvement was gained during the extension phase. And finally, the overall completion rate was 1.3%, requiring unrealistic extrapolation to draw meaningful conclusions. Keck et al. [39,40] mention lack of generalizability as a potential limitation of the enrichment design, but they do not discuss how these other limitations may have compromised the trial's internal validity.

The FDA's review of the Keck trial identified other substantive concerns, including the fact that the *p*-value for the primary analysis changed from 0.02 to 0.10 when the statistical reviewer excluded data from one of the trial's two Mexican sites (where the relapse rate among participants in the aripiprazole arm was lower than the other trial sites) [46]. While of general concern, this and other issues identified by the FDA are unrelated to our methodological critiques. All of these factors undercut even a cautious interpretation of the Keck trial as supporting the use of aripiprazole for maintenance treatment of bipolar disorder. Below we review each of these criticisms in detail.

Insufficient duration to demonstrate prophylactic efficacy. In the open-label phase of the Keck trial, stability was defined by whether or not a participant maintained YMRS and MADRS scores in the asymptomatic range for at least 6 consecutive weeks. To meet this criterion, on average the trial participants spent 89 d in the stabilization phase. Comparing their own work to other randomized discontinuation studies of maintenance treatment in bipolar disorder that required a shorter duration of stability [47–49], Keck et al. describe their stability criterion as "the most stringent criteria to date to define stability" (p. 634) [39]. Intervention-arm participants who had achieved stability on aripiprazole were then assigned to continue with aripiprazole, and placebo-arm participants abruptly switched to placebo, for the following 26 wk.

Contrary to the authors' claims, we argue here that, given the natural history of bipolar disorder, the design of the Keck trial was unsuitable for evaluating the efficacy of aripiprazole in the maintenance treatment of bipolar disorder. The episodic nature of recurrent mania and depression require investigators to randomize, enroll, and retain patients for a duration sufficient to demonstrate maintenance and/or prophylactic efficacy. While there is high interindividual variation, the median length of untreated episodes has been reported to vary from 3–6 mo in clinical trial settings and from 2–3 mo in epidemiological studies [50], with depressive episodes typically lasting longer than manic episodes [21,51]. Thus, even if one does not accept the other methodological concerns we describe in this paper, the Keck trial, with its stabilization criterion of 6 wk, could at best be used to demonstrate a short-term benefit of continuation treatment in preventing relapse of symptoms attributable to an ongoing acute episode [52]. Demonstration of maintenance efficacy in preventing recurrence of mood episodes would require benefit to be shown at least 6 mo after the acute phase. 6 mo has been traditionally recognized as the point at which continuation treatment becomes maintenance treatment [10,11,12,52–54]. Appropriately, the clinical review contained in the supplemental NDA describes a meeting with the study's sponsors in which the FDA's Division of Neuropharmacological Drug Products "expressed that the duration of the open-label stabilization phase defines duration of effect and noted that an optimal study design would include a six month open-label stabilization phase and randomized withdrawal of patient subgroups at specified timepoints" (p. 9) [55]. The leading textbook in the field suggests an even more stringent threshold study duration: "Because the natural history of bipolar disorder is for it to recur, on average, every 16–18 months, true prophylaxis cannot be evaluated in 6 or 12 months" (p. 801) [21]. Although somewhat controversial, the idea that demonstration of true prophylactic efficacy requires a study duration longer than that which has been typically utilized has been supported by other leading researchers as well [11,52,56].

Limited generalizability due to the enriched sample. Only participants who had responded to aripiprazole in the stabilization phase of the trial were included in the double-blind phase of the trial. Of the 567 participants who entered the stabilization phase, only 206 completed it. Some of the randomized participants received unblinded medication and were therefore discontinued [29], so the double-blind efficacy dataset consisted of 161 participants. This means that 361 of the 567 (74%) participants who entered the stabilization phase but dropped out were excluded from randomization because of adverse events, lack of efficacy, withdrawal of consent, and other reasons as detailed in the publication—leaving behind a selected group of participants who had responded favorably to aripiprazole in the stabilization phase to be subsequently randomized. This design could have the effect of biasing the trial's findings away from the null [57], and, even in the absence of such bias, the results from this enriched sample cannot be generalized to the majority of persons diagnosed with bipolar disorder. This limitation of the randomized discontinuation design has long been recognized by drug trialists [11,12,56,58–65] and is not dissimilar to criticisms voiced about the first generation of randomized trials evaluating the use of lithium for maintenance treatment in bipolar disorder, i.e., that those study designs selected preferentially for lithium-responsive variants of the disorder [66,67].

Possible conflation of iatrogenic effects with beneficial effects. The randomized discontinuation study design could explain the putatively positive findings on preventing relapse even in the absence of a true drug effect. In the Keck trial, the randomization sample was enriched with participants who had already responded to aripiprazole in the stabilization phase and were therefore more likely to experience an iatrogenic relapse of symptoms when aripiprazole was abruptly discontinued in the double-blind phase. Abrupt discontinuation, or even abrupt partial removal, of a drug used for maintenance has long been known to provoke relapse in patients diagnosed with bipolar disorder [68–77]. This "bipolar rebound phenomenon" has been most often described for lithium, but it has also been observed in the setting of abruptly withdrawn antiepileptic [78], antipsychotic [3,12,48,56,78–80], and antidepressant medications [59,75,78,81] administered to persons diagnosed with other mood and psychotic disorders. For this reason, Geddes et al. specifically excluded studies with a randomized discontinuation design from their systematic review and meta-analysis of the long-term use of lithium in the treatment of bipolar disorder [82].

Thus, if aripiprazole had no effect on preventing relapse, the Keck trial might still be expected to show a higher relapse rate early in the double-blind phase among participants assigned to the placebo arm (compared to those assigned to the intervention arm), and then similar relapse rates between study arms during the extension phase. This particular design element appears to have substantially influenced the outcome of the Keck trial, as is evident from a comparison of data from the 26-wk double-blind phase with data from the 74-wk extension phase. During the 26-wk double-blind phase, 19 out of 83 participants (23%) in the placebo arm experienced a manic relapse, whereas only four (5%) did so in the subsequent 74-wk extension phase.

When relapse data from the 74-wk extension phase are examined separately from those from the first 26 wk (Figure 3), only four participants in the placebo arm experienced a relapse to mania, compared to 3 participants in the intervention arm (4.8% versus 3.8%). This information is not explicitly presented in either paper and can only be discerned by comparing the papers side by side and calculating the differences by hand. Figure 4 in the 74-wk extension phase publication (p. 1486) [40] shows that 28% of participants in the placebo arm relapsed to mania over 100 wk of follow up. Given $n = 83$ in the placebo arm, this suggests 23 participants in the placebo arm relapsed to mania over 100 wk of follow up. Because 19 participants in the placebo arm relapsed to mania in the first 26 wk (Figure 5 in the 26-wk double-blind phase publication [p. 531] [39]), this means four participants relapsed to mania during the 74-wk extension phase. We employed similar reasoning to calculate the number of participants who relapsed to mania in the intervention arm, as well as the number of participants who relapsed to depressive and mixed states. Similar patterns are observed for relapse to depression and relapse to mixed state for the placebo and aripiprazole arms. Thus, virtually all of the reported placebo-aripiprazole difference in relapse occurred during the first 26 wk of the trial.

Limitations of the low completion rate. Only seven of 39 (18%) aripiprazole-treated participants and five of 27 (19%) placebo-treated participants completed the 74-wk extension phase. The low completion rate in the treatment arm is especially striking given that only participants who had proven to be responders in the initial stabilization phase were included in the double-blind and extension phases and that the placebo group matched the aripiprazole group in terms of trial completion. Out of the 633 participants who entered the trial, after excluding the 83 who were switched to placebo, only seven aripiprazole-treated participants completed the 100-wk trial, for a completion rate among aripiprazole-treated participants of less than 1.3%. This is not explicitly noted anywhere in the paper [40]. Keck et al. [40] acknowledge that only 12 participants completed the trial, but the smaller denominator used for comparison is the number of participants who entered the 74-wk extension phase rather than all participants who entered the trial.

We argue that drawing meaningful conclusions from a trial with an overall completion rate of less than 1.3% is an inappropriate undertaking. The completion rate substantially limits generalizability of the trial's findings, as trial completers very likely were dissimilar to the enrolled and/or randomized participant pools. The meaningful differences between completers and noncompleters were demonstrated in a randomized trial of divalproex versus

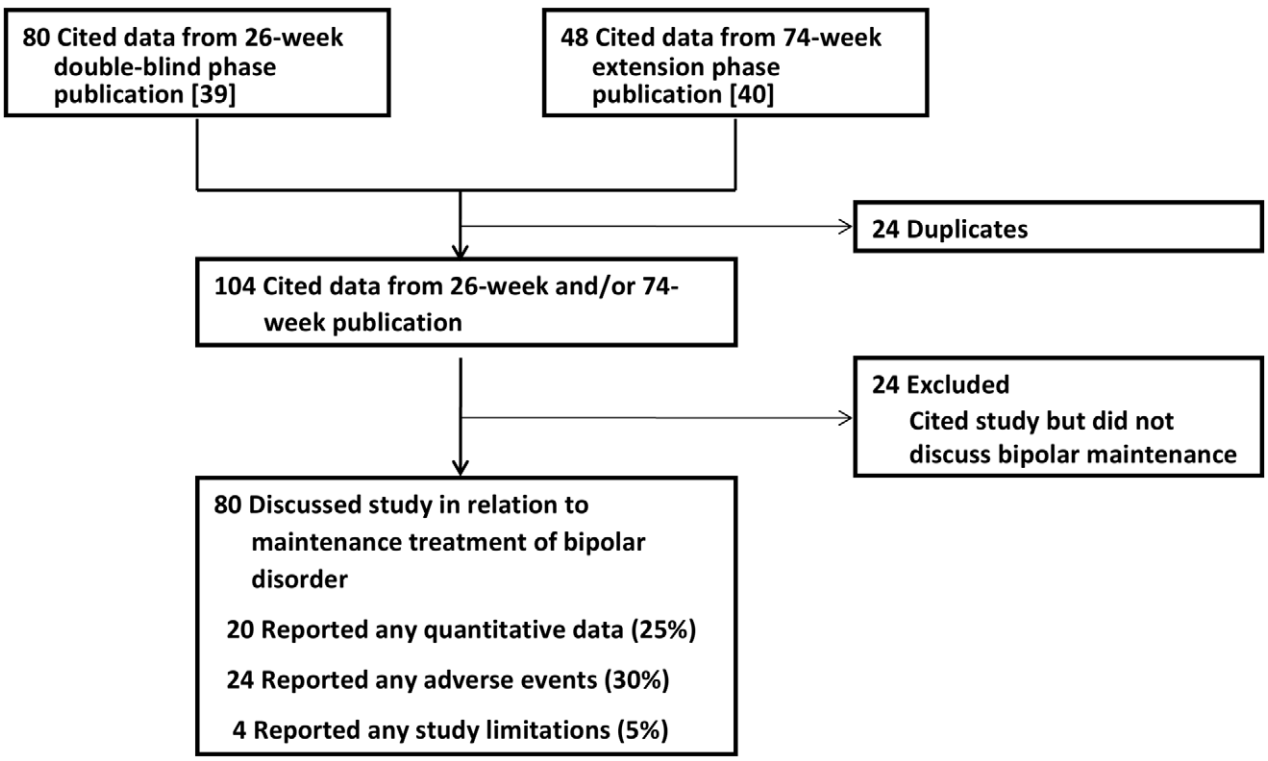

Figure 4. Publications citing the Keck study. These publications were identified using Web of Science(R) Science Citation Index Expanded. Those that discussed the Keck study in relation to the maintenance treatment of bipolar disorder were evaluated on three quality indicators, as shown.
doi:10.1371/journal.pmed.1000434.g004

lithium for relapse prevention in bipolar disorder [83]: participants who completed the trial had milder symptoms at baseline and a less severe lifetime illness course [84]. Keck et al. identify the low completion rate in the extension phase as a potential limitation but appeal to the low completion rates observed in other maintenance trials [47,48] to support the generalizability of their results. In contrast, we view the similar completion rates observed in other long-term studies as similarly raising concerns about how to draw inferences from these trials to inform routine clinical practice. Still, we observe that other investigators have successfully implemented long-term studies in this patient population with greater rates of completion: for example, earlier studies of lithium in the treatment of affective disorders demonstrated completion rates of 92.9% (26/28) [85] and 73.2% (74/101) [86] among lithium-treated participants.

Impact of the Keck Trial on the Literature

Our citation search protocol identified 80 articles that cited the results from the 26-wk double-blind phase [39] and 48 articles that cited the results of the 74-wk extension phase [40]. After eliminating duplicates, the two publications from the Keck trial garnered 104 subsequent citations in total. Of these citing articles, 24 did not contain any mention of the Keck trial in relation to long-term or maintenance treatment of bipolar disorder and were excluded from further analysis (Figure 4). Double-coding revealed a high degree of inter-rater agreement on the quality assessment measures. There was 100% agreement on whether the publications were classified as mentioning aripiprazole for maintenance treatment. Among the double-coded publications mentioning maintenance treatment, there was 100% agreement on whether quantitative data and limitations were mentioned. There was one disagreement about whether adverse events were mentioned, yielding a kappa coefficient of 0.75 (95% CI 0.05–0.95). The overall kappa coefficient was 0.95 (95% CI 0.73–0.99).

Of the 80 articles that cited the Keck trial in reference to maintenance treatment of bipolar disorder, only 20 (25%) presented any quantitative data from the Keck trial; the remainder reported qualitative statements only (e.g., "Aripiprazole significantly delayed the time to relapse into a new mood episode in patients with bipolar I disorder over both 26 and 100 weeks of treatment." [87]). 24 publications (30%) mentioned any of the adverse events reported in the trial. Only four (5%) made any mention of study limitations.

Among the articles identified through our citation search protocol were eight literature reviews [88–95] and three bipolar treatment guidelines [15,96,97] that specifically discussed the use of aripiprazole in the treatment of bipolar disorder. Because review articles and treatment guidelines can be particularly influential in shaping policy and prescribing behavior, we chose to highlight these in our discussion (Table 1). The evidence summaries employed the methodologies of consensus panel ($n = 3$), narrative review ($n = 6$), or systematic review ($n = 2$). Ten of the 11 reviews and treatment guidelines contained a financial disclosure related to Bristol-Myers Squibb.

Overall, the eight reviews were favorable in their assessment as to the putative efficacy of aripiprazole in the maintenance treatment of bipolar disorder. Solely on the basis of the results of the Keck trial, the Texas Medication Algorithm Project update listed aripiprazole as having "level 2" evidence (out of five levels of quality, with level 1 being the highest-quality) for maintenance treatment of bipolar disorder [15]. The Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders recommended aripiprazole as first-line maintenance treatment of bipolar disorder, although it is noted that this is "mainly for preventing mania" (p. 235) [96]. This treatment recommendation was based on the Keck trial, along with a 30-wk pediatric bipolar trial that has only been published in abstract form [98]. The British Association for Psychopharmacology (BAP) based its positive endorsement of aripiprazole for relapse prevention solely on the Keck trial [97]. Contrary to the criticisms we described earlier, the BAP guidelines note, "Acute withdrawal of the active agent did not produce an excess of early relapse in this study" (p. 26).

Discussion

Our evaluation of the evidence base supporting the use of aripiprazole for the maintenance treatment of bipolar disorder reveals that the justification for this practice relies on the results from a single trial by Keck and colleagues published in two peer-reviewed journal articles [39,40]. The methodology and reporting of the Keck trial are such that the results cannot be generalized to inform the treatment of most patients with bipolar disorder. Published interpretations of the data notwithstanding, in our opinion the Keck trial does not provide data to support the use of aripiprazole in the maintenance treatment of bipolar disorder. This lack of robust evidence of benefit should be weighed against the potential for long-term harms that have been described with other antipsychotic medications [3] and adverse events related to aripiprazole use, including tremor, akathisia, and significant weight gain [39]. Our concern about the critical imitations in this trial is further accentuated by the apparent widespread use of aripiprazole as a first-line agent for the maintenance treatment of bipolar disorder [31,32].

Although we appreciate that the unique clinical features of bipolar disorder make controlled study extremely difficult [67,84,99–103], many of the weaknesses we document stem from the use of the randomized discontinuation design. Further study is needed in order to determine whether the problems described in this particular case are also more widely applicable to other continuation or maintenance treatment studies in bipolar disorder. We find unpersuasive the argument that a randomized discontinuation study such as this is valuable because it reflects common clinical practice [104,105]. The two-arm, parallel randomized controlled trial may yield information that is more clinically useful than the discontinuation design. Under the parallel design, data from all participants (not just those who demonstrated an acute response) would contribute to our understanding of the drug's short- and long-term efficacy: one of two medications (or placebo) would be given to participants in the acute phase, and they would be followed throughout the continuation and maintenance phases (and beyond) to document response to treatment. (This study design, as well as the other study designs we describe, clearly could be used to study nonpharmacological treatments, including evidence-based psychotherapies. However, because this paper has emphasized discussion about pharmacologic treatments, we use the phrase "medication" for simplicity.) A two-arm, parallel randomized controlled trial of sufficient duration would directly answer the substantive research question, "Does aripiprazole treat symptoms to remission and prevent recurrent episodes when given to patients diagnosed with bipolar disorder presenting in a manic or mixed state?" This is clearly different from the question answered by the discontinuation design, "Among patients diagnosed with bipolar presenting in a manic or mixed state who have achieved a reasonable symptomatic improvement after being given aripiprazole, should aripiprazole be continued to maintain the initial improvement?" [106].

Table 1. Treatment guidelines and reviews of aripiprazole for the treatment of bipolar disorder.

Author, Year, Country	Financial Disclosure Related to Bristol-Myers Squibb	Methods	Quality Indicators[a]			Narrative Recommendation
			A	B	C	
Goodwin, 2009, Great Britain [97]	Yes	Consensus panel	No	No	No	"Aripiprazole was more effective than placebo after acute and continuation treatment of mania with aripiprazole: no effect on depression was discernable. Acute withdrawal of the active agent did not produce an excess of early relapse in this study." **(positive)**
Yatham, 2009, Canada [96]	Yes	Consensus panel	No	No	No	"Given that efficacy was shown primarily for mania, aripiprazole is included as a first-line maintenance treatment for bipolar disorder for the treatment and prevention of mania." **(positive)**
Suppes, 2005, United States [15]	Yes	Consensus panel	No	No	No	"Aripiprazole is recommended based on a randomized, double-blind, placebo-controlled, 6-month maintenance study in which patients received open-label aripiprazole until stable, then were randomized to either placebo or aripiprazole for the 6-month follow-up." **(positive)**
Garcia-Amador, 2006, Spain [93]	Yes	Narrative review	Yes	Yes	No	"These data support the decision by the US FDA to approve aripiprazole for the maintenance treatment of bipolar patients, beyond the treatment of acute mania." **(positive)**
McIntyre, 2007, Canada [91]	Yes	Narrative review	Yes	Yes	No	"Aripiprazole is established as being efficacious in acute mania and for the prevention of manic relapse in BD. Aripiprazole efficacy is confirmed on primary and secondary efficacy parameters." **(positive)**
Fagiolini, 2008, United States [94]	Yes	Narrative review	Yes	Yes	No	"This 100-week study showed a significantly longer time to relapse with aripiprazole when compared with placebo." **(positive)**
McIntyre, 2007, Canada [90]	Yes	Narrative review	Yes	Yes	No	"A single, randomized, double-blind, parallel group, placebo-controlled study reported on the safety and efficacy of aripiprazole in preventing relapse of a mood episode in recently manic or mixed episode patients with bipolar I disorder." **(positive)**
Ulusahin, 2008, Turkey [95]	None disclosed	Narrative review	Yes	Yes	No	"One double-blind, randomized, placebo controlled clinical trial of 100-week aripiprazole monotherapy, which is the longest clinical trial among the trials conducted in bipolar disorder among the second-generation antipsychotics, showed that aripiprazole was effective for relapse prevention in bipolar patients." **(positive)**
Muzina, 2009, United States [89]	Yes	Narrative review	Yes	Yes	No	"The results from a 100-week study of aripiprazole for the prevention of bipolar I episodes represent the longest maintenance study since early lithium trials and support the use of aripiprazole as maintenance treatment, primarily against manic relapses." **(positive)**
Fountoulakis, 2009, Greece [88]	Yes	Systematic review	Yes	Yes	Yes	"Recent reviews suggest that aripiprazole is efficacious in acute mania and in the maintenance treatment of bipolar disorder, with a favourable safety and tolerability profile, with minimal propensity for clinically significant weight gain and metabolic disruption." **(positive)**
McIntyre, 2010, Canada [92]	Yes	Systematic review	Yes	Yes	Yes	"The available evidence supports the efficacy and tolerability of aripiprazole in the maintenance treatment of bipolar disorder." **(positive)**

[a]A, reported any quantitative data; B, reported any adverse events; C, reported any study limitations.
BD, bipolar disorder.
doi:10.1371/journal.pmed.1000434.t001

The primary disadvantage of the parallel design is that a greater proportion of (acutely ill) study participants would be subjected to placebo for the full duration of the trial, exactly the ethical issue that the discontinuation design was intended to address [107,108]. Keck et al. [39] stated that they sought to minimize the extent to which stabilized participants were administered placebo. Yet their study could have been modified to diminish its exposure to the weaknesses that we have described above. First, the duration of stability required prior to randomization could be lengthened. One likely cost of this design modification is that the proportion of participants actually randomized would decrease further [109]. A second modification would be to gradually taper the discontinuation of medication among participants randomized to receive placebo. In previously published randomized discontinuation studies, medications administered during the open-label phase were tapered over a period of 2 to 3 wk rather than abruptly discontinued [47,83]. Greenhouse et al. [59] suggest implementing the taper over several months.

Aside from these modifications to the parallel design, other alternatives have been suggested. Greenhouse et al. [59] proposed an alternative randomization scheme in which study participants are randomized to one of six treatment strategies. In the acute phase of treatment, study participants would receive one of two medications. In the maintenance phase of treatment, study participants would either remain on the medication initiated during the acute phase, be switched (gradually) to the alternative medication, or be switched (gradually) to placebo. This innovative study design would address the substantive research question, "Which treatment strategy is better in controlling and preventing the recurrence of depression?" (p. 318) [59]. A pure prophylactic design has also been recommended [10,12,100], in which patients previously diagnosed with a recurrent mood disorder would be enrolled during a medication-free remission period. Then, while participants are in remission, they would be offered one of two medications (or placebo). All participants would be followed in the study for a prespecified duration, and the treatment arms would be compared in terms of time to recurrence of a mood episode. This design would avoid the previously described error of possibly conflating beneficial treatment effects with iatrogenic adverse effects of abrupt medication discontinuation. However, as noted by Goodwin, Whitman, and Ghaemi [12], the failure of the divalproex study by Bowden et al. [83] was partly attributed to its enrollment of participants with low severity of illness [84]—and it was the last study to utilize the lithium-era prophylaxis design.

We recognize that the proposed study designs will be regarded by some as too costly or infeasible. Although some have suggested that a study with selected limitations may be useful in guiding clinical practice [104], we would disagree with this argument. The current "anti-Hippocratic" state of psychopharmacological practice described by Ghaemi [56,110] raises questions about the extent to which research with substantive limitations is appropriately interpreted with conservative sensibilities. These concerns are borne out in our data. Thomson Reuters Essential Science Indicators(SM) places the 26-wk double-blind phase publication in the top 1%, and the 74-wk extension phase publication in the top 1%–2%, of papers published in the fields of psychiatry and psychology. Thus, by our conservative estimates, the Keck trial could be regarded as relatively influential. More importantly, we found that the Keck trial was cited uncritically by a subsequent generation of authors, through treatment guidelines, reviews, and other publications. All failed to note the consequences of abrupt and premature discontinuation of antimanic medication, especially during the vulnerable continuation period. The uncritical manner in which the Keck trial has been cited is reminiscent of the "echo chamber" effect described by Carey et al. [111] in their assessment of the now-discredited use of gabapentin in the treatment of bipolar disorder. Although the analogy is somewhat limited as there were no reportedly positive double-blind trials examining the use of gabapentin for this indication, we document a similar pattern of uncritical citations of the primary evidence regarding aripiprazole in the maintenance treatment of bipolar disorder.

Of further concern regarding the uncritical citation of the Keck trial's claims is that ten of the 11 treatment guidelines and review articles in our sample contained a financial disclosure related to the drug's manufacturer, Bristol-Myers Squibb Co. Financial conflicts of interest are highly prevalent across a wide range of medical subfields [112], and while they are known to be associated with recommendations in review articles [113], there is no systematic research documenting their influence on clinical practice guideline recommendations [114]. However, financial conflicts of interest have been found to be associated with biased reporting of outcomes in randomized trials [115,116], which serve as the evidence upon which treatment guideline recommendations are based.

In summary, we provide here a critical appraisal of the available evidence regarding the use of aripiprazole for the maintenance treatment of bipolar disorder. The available evidence consists of a single trial by Keck et al. [39,40], which is subject to several substantive methodological limitations but has nonetheless been cited uncritically in the ensuing scientific literature. Several alternative modifications or study designs may improve the probability of generating more useful data from studies in this vulnerable patient population to inform the treatment of similar patients in the future. We are concerned that the publication and apparently uncritical acceptance of this trial may be diverting patients away from more effective treatments.

Supporting Information

Table S1 Published studies excluded from review. These five published studies were not included in the review because they were open-label, examined the use of aripiprazole as adjunctive treatment or for acute mania, or lacked sufficient duration.
Found at: doi:10.1371/journal.pmed.1000434.s001 (0.03 MB DOC)

Table S2 Clinical trial registry studies excluded from review. These 12 studies were not included in the review because they were open-label, examined the use of aripiprazole as adjunctive treatment or for acute mania, or lacked sufficient duration.
Found at: doi:10.1371/journal.pmed.1000434.s002 (0.04 MB DOC)

Text S1 Approval package for: 21-436/S-005 & S-008 & 21-713/S-003. Washington (D.C.): Center for Drug Evaluation and Research, U.S. Food and Drug Administration; 2005. This supplemental New Drug Application (sNDA), which provides for the use of aripiprazole as maintenance therapy in bipolar I disorder, was obtained through a U.S. Freedom of Information Act request.
Found at: doi:10.1371/journal.pmed.1000434.s003 (4.92 MB PDF)

Acknowledgments

The authors thank Anne Ludvik of the library service at the San Francisco Veterans Affairs Medical Center, for help in crafting the evidence search protocols and the citation search protocol; five reviewers, for helpful suggestions; and Tom Zamojcin at Thomson Reuters, for providing the Essential Science Indicators data.

Author Contributions

ICMJE criteria for authorship read and met: ACT NZR JNJ PIP GIS DH. Agree with the manuscript's results and conclusions: ACT NZR JNJ PIP GIS DH. Designed the experiments/the study: ACT NZR. Analyzed the data: ACT NZR JNJ GIS DH. Collected data'did experiments for the study: ACT NZR. Wrote the first draft of the paper: ACT NZR. Contributed to the writing of the paper: ACT NZR JNJ PIP GIS DH. Contributed to the concept and design of the paper and first draft: PIP.

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Editors' Summary

Background. Bipolar disorder (manic depression) is a serious, long-term mental illness that affects about 1% of adults at some time during their life. It usually develops in late adolescence or early adulthood and affects men and women from all backgrounds. People with bipolar disorder experience wild mood swings that interfere with daily life and damage relationships. During "manic" episodes, which can last several months if untreated, they may feel euphoric ("high"), energetic, or irritable. They may be full of ambitious plans, feel creative, and spend money recklessly. They can also have psychotic symptoms—they may see or hear things that are not there. During depressive episodes, affected individuals may feel helpless, worthless, and suicidal. Treatments for bipolar disorder include drugs to stabilize mood swings (for example, lithium and anticonvulsant medications), antidepressants to treat depressive episodes, and antipsychotic drugs to treat manic episodes. Psychotherapy can also help and patients can be taught to recognize the signs of approaching manic or depressive episodes and the triggers for these episodes.

Why Was This Study Done? Treatment of bipolar disorder is divided into three phases: acute treatment lasting about 2 months to achieve remission, continuance treatment lasting from months 2 through 6 to prevent relapse, and long-term maintenance treatment to prevent recurrence. Second-generation (atypical) antipsychotics are widely used for acute treatment of manic episodes but are also used for maintenance treatment. For example, the atypical antipsychotic aripiprazole, which gained US approval for this indication in 2005, is now a popular choice among clinicians for treating bipolar disorder. But how much evidence is there to support aripiprazole's use in the maintenance treatment of bipolar disorder? Here, the researchers systematically search the published literature for double-blind randomized controlled trials of aripiprazole for this indication, critically analyze the quality of these trials, and undertake a citation search to investigate how the results of these trials have been disseminated in the scientific literature. In double-blind randomized controlled trials, patients are randomly assigned to receive a test drug or a control (generally, placebo), and the effects of these drugs compared; patients in the trial, and physicians administering treatments, would not know who is receiving the test drug or control until the trial is completed.

What Did the Researchers Do and Find? The researchers' search for reports of double-blind randomized controlled trials of aripiprazole for the maintenance treatment of bipolar disorder using predefined criteria identified only two publications, both describing a single trial—the Keck trial. Critical review of this trial identified four issues that limit its interpretation for supporting aripiprazole as a maintenance therapy: the trial was too short to demonstrate maintenance efficacy; all the trial participants had responded well to aripiprazole as an acute treatment so the generalizability of the trial's results was limited; the trial design meant that some of the apparent beneficial treatment results could have reflected the adverse effects of abrupt medication discontinuation in the control group; and the trial had a low completion rate. The researchers' citation search identified 80 publications that cited the Keck trial in discussions of the use of aripiprazole for maintenance treatment of bipolar disorder. Only a quarter of these papers presented any numerical data from the trial, only a third mentioned any of the reported adverse events, and only four papers mentioned the trial's limitations.

What Do These Findings Mean? This evaluation of the evidence base supporting the use of aripiprazole for the maintenance treatment of bipolar disorder shows that the justification for this practice relies on the results of one published trial. Moreover, the methodology and reporting of this trial mean that its results cannot easily be generalized to inform the treatment of most patients with bipolar disorder. Worryingly, the researchers' citation search indicates that the Keck trial has been cited uncritically in the ensuing scientific literature. Although the unique features of bipolar disorder make it hard to undertake controlled studies of treatment options, the researchers express concern that "the publication and apparently uncritical acceptance of this trial may be diverting patients away from more effective treatments".

Additional Information Please access these websites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1000434.

- The US National Institute of Mental Health has detailed information on bipolar disorder, including an Easy to Read booklet (in English and Spanish)
- The UK National Health Service Choices website provides information on all aspects of bipolar disorder
- The UK charity Mind has information on bipolar disorder and provides links to other useful organizations
- MedlinePlus has links to further information on ><bipolar disorder (in English and Spanish)

BOOK REVIEW

Your child does not have bipolar disorder: how bad science and good public relations created the diagnosis (childhood in America)

Stuart L. Kaplan

Santa Barbara: Praeger, 2011
ISBN: 978-0-313-381348, 184 pp. Hard cover $34.95. Ebook 9780-313-38135-5.

Many Australasian psychiatrists may wonder why a book would need to be titled "Your child does *not* have bipolar disorder", but those familiar with child psychiatry in the USA would recognize such a book is aimed at an American readership. For years, American bookstores have been awash with titles such as *The Bipolar Child*, *Bipolar Not ADHD*, *Parenting A Bipolar Child*, *Bipolar Kids*, *The Ups and Downs of Raising a Bipolar Child*, *Is your Child Bipolar?* and innumerable others. Additionally, bedtime reading books for very young "bipolar" children abound e.g. *Brandon and the Bipolar Bear*, *The Storm in my Brain* and *My Roller Coaster Bipolar Feelings Workbook*. Standing lonely on the shelves now is this contrarian perspective from an experienced professor of child psychiatry from Pennsylvania, Stuart L. Kaplan.

Kaplan has gone out on a limb in American psychiatry where pro-paediatric bipolar disorder (PBD) articles dominate the journals. But he does echo the opinion piece by Allen Frances, DSM-IV task force head, who laid the blame for the "epidemic" of childhood bipolar in the USA upon "thought leading researchers" who ignored strict DSM-IV criteria, the influence of the pharmaceutical industry, a pressing need for parents to manage children's behavioural problems, and "advocacy groups, the media, the internet and numerous books aimed at suffering parents".[1]

Kaplan subtitles his book *How Bad Science and Good Public Relations Created the Diagnosis* and in clear prose directed at the educated parent or teacher, but also highly referenced for the health professional, he dissects the PBD science and finds it lacking. Kaplan expands on Frances' critique of PBD researchers having strayed from DSM-IV criteria. A thread throughout is that existing DSM diagnoses of ADHD and oppositional defiant disorder (ODD) are generally sufficient.

Kaplan describes the evolution of PBD from the mid 1990s when "two distinguished child psychiatrists, Joseph Biederman (Harvard) and Barbara Geller (Washington University in St Louis) independently began to report there was something more than ADHD and ODD … troubling school aged children and adolescents. The additional crucial diagnosis was … bipolar disorder" (p. 24).

There follows a critique of several highly influential PBD research articles that makes one wish he'd been involved in the original peer reviews. Significant research was predicated upon parent informants to structured interviews where "incredibly [researchers] did not interview the child patients" (p. 25). In a section on "one authoritative view" (p. 35), Kaplan pays homage to Carlson, one of the few authors of sceptical PBD articles, who has strongly critiqued the parent informant rating scale approach.[2] He goes on to review the bipolar offspring literature that fails to find pre-pubertal cases, the genetics literature still in its infancy, and the retrospective recall and epidemiological literature that reflects the assumptions of researchers; large studies like the Smoky Mountains study didn't find pre-pubertal cases.

A chapter on "cultural influences" notes the power of the media, in particular the best-selling book *The Bipolar Child* by Papolos and Papolos being highlighted by the *Oprah Winfrey Show*, *Time* magazine and others. The pivotal role of advocacy groups is also explored and there is mention of the vagaries of diagnostic up-coding in the US health system. Kaplan makes only passing reference to the influence of the pharmaceutical industry, though their influence of advocacy groups and research has been highlighted elsewhere.[3,4] In chapters on pharmacotherapy and a critique of PBD drug trials, he emphasizes the increased efficacy and safety of stimulants (often out of favour as parents and clinicians fear precipitating mania) for ADHD versus anticonvulsants, antipsychotics and lithium for misdiagnosed PBD. He appeals to parents to consider stimulants, and "family-based behavioural modification programs".

Whilst the main focus is the epidemic of pre-pubertal diagnosis, adolescent over-diagnosis is discussed in the chapter "Did Romeo and Juliet have bipolar II disorder?"

Perhaps treading gently with parents in mind as his main readership, Kaplan doesn't explore the effects of maltreatment, developmental trauma and attachment disruption, nor the social stress on modern families. There is a vast literature in this area and it can be argued that many "bipolar kids" with their extreme moodiness would be better described as suffering "developmental trauma disorder",[5,6] where stimulants may still have symptomatic benefit, but deeper dyadic psychotherapies and parent training approaches offer further promise. In an afterword,

Sharna Olfman, who edits the "Childhood in America" series of which Kaplan's book is the latest, does highlight these issues.

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.[7] 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.

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doi: 10.3109/10398562.2011.608222

Journal of Trauma & Dissociation, 13:51–68, 2012

ISSN: 1529-9732 print/1529-9740 online
DOI: 10.1080/15299732.2011.597826

Routledge
Taylor & Francis Group

Pediatric Bipolar Disorder in an Era of "Mindless Psychiatry"

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Objective: *Pediatric bipolar disorder (PBD) reflects shifts in conceptualizing bipolar disorder among children and adolescents since the mid-1990s. Since then, PBD diagnoses, predominantly in the United States, have increased dramatically, and the diagnosis has attracted significant controversy. During the same period, psychiatric theory and practice has become increasingly biological. The aim of this paper is to examine the rise of PBD in terms of wider systemic influences.* Method: *In the context of literature referring to paradigm shifts in psychiatry, we reviewed the psychiatric literature, media cases, and information made available by investigative committees and journalists.* Results: *Social historians and prominent psychiatrists describe a paradigm shift in psychiatry over recent decades: from an era of "brainless psychiatry," when an emphasis on psychodynamic and family factors predominated to the exclusion of biological factors, 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*

Received 28 October 2010; accepted 3 March 2011.

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system that favors "diagnostic upcoding." Harm from overmedicating children is now a cause of public concern. Conclusion: *It can be argued that PBD as a widespread diagnosis, particularly in the United States, reflects multiple factors associated with a paradigm shift within psychiatry rather than recognition of a previously overlooked common disorder.*

KEYWORDS affective disorders, attachment, behavioral disorders, behavioral medicine, emotion regulation, childhood trauma, professional attitudes, diagnostic validity, pediatric illness, DSM *validity*

BACKGROUND

It has long been accepted that bipolar disorder has its peak onset in late adolescence to young adulthood. It is also true that early episodes of hypomania can be difficult to diagnose. However, Biederman and colleagues (Wozniak et al., 1995) proposed that *most* cases of bipolar disorder have a preschool age onset and that irritability, not elevated mood, is the core feature. Such children were described as presenting "as irritable, with 'affective storms' or prolonged and aggressive temper outbursts" and with "chronic and continuous rather than episodic and acute" clinical course (Biederman et al., 1996, p. 998). In the same year, Geller and colleagues (1995), in another departure from traditional concepts of manic depressive illness, proposed that most cases of bipolar disorder in children still exhibited elevated mood but also featured ultradian mood cycles—several cycles of mania and depression per day. Geller and Luby (1997), in a review article in the *Journal of the American Academy of Child and Adolescent Psychiatry* (*JAACAP*), stated,

> 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)

Over the next decade these pediatric bipolar disorder (PBD) constructs gained acceptance in the United States. Another review article in *JAACAP* (Pavuluri, Birmaher, & Naylor, 2005) noted that the National Institute for Mental Health roundtable on pre-pubertal PBD, convened in April 2000, had termed the chronic irritable mood group *broad phenotype PBD* and the elevated mood group *narrow phenotype PBD*. When *JAACAP* published

"Treatment Guidelines for Children and Adolescents with Bipolar Disorder" (Kowatch et al., 2005), a commentary (McClellan, 2005) raised doubts about the diagnostic validity of PBD, but skeptical articles in the literature were few. Biederman (2006), although acknowledging the debate over the validity of PBD, asserted that the literature supported the diagnosis and that "up to 20% of psychiatrically referred children satisfy criteria for bipolar spectrum disorders" (p. 901).

However, follow-up studies have shown that non-episodic irritable broad phenotype PBD does not progress to adult bipolar disorder, and thus it has been relabeled *severe mood dysregulation* (Stringaris et al., 2010). This may have tempered the spread of PBD diagnoses; nonetheless, publications like the recent book *Is Your Child Bipolar?* (Wozniak & McDonnell, 2008), reviewed by Levin (2010), still propound the broad as well as narrow versions of PBD.

PBD was popularized to the public in the bestselling book *The Bipolar Child: The Definitive and Reassuring Guide to Childhood's Most Misunderstood Disorder* (Papolos & Papolos, 2000) and as the cover story of *Time* magazine (Kluger & Song, 2002). Both the book and the article suggested that bipolar disorder could begin in utero. Advocacy groups like the Child and Adolescent Bipolar Foundation (www.bpchildren.com) and the Juvenile Bipolar Research Foundation (www.jbrf.org) provided parent education and an online diagnostic questionnaire.

Upon this background, diagnoses of bipolar disorder in children and youth increased 4,000% from 1994–1995 to 2002–2003 (Moreno et al., 2007), and by 2004 PBD had become the most common diagnosis in U.S. prepubertal psychiatric inpatient units (Blader & Carlson, 2007).

However, after 15 years PBD remains a contentious diagnosis. Its validity is questioned both academically (Frances, 2010; Parens & Johnson, 2010) and increasingly in the public media through stories of heavily medicated children and conflicts of interest involving researchers and the pharmaceutical industry.

Psychiatry is as much social science as a biomedical discipline, and its tenets are subject to influence by the prevailing paradigm. We believe the phenomenon of PBD as a new, commonly used diagnostic entity confined mainly to the United States is best comprehended from a broad systemic perspective. Such a perspective needs to explore beyond the PBD academic literature with its focus on symptom cluster analyses, neuroimaging, and medication responses to consider overarching paradigmatic shifts in psychiatry, particularly shifts in nosology and research methodology, individual and societal repression of trauma, the vagaries of managed care in the U.S. health system, and the influence of the pharmaceutical industry.

This article therefore takes a narrative approach. We acknowledge our skepticism, which is based on our clinical experience, reading of the literature and wider media, and communication with colleagues. Differences

in practice and training between the United States and other countries are factored in, with a focus on differences where we work—Australia (Peter Ignatius Parry) and the United States (Edmund C. Levin).

MEDIA CASES

The media have reported several cases of the overmedication of very young children featuring the PBD diagnosis. The story of Rebecca Riley, diagnosed at age 2 and deceased from a medication overdose at age 4, is widely known (CBS *60 Minutes*, 2007). Although Rebecca died after her parents allegedly gave extra clonidine plus a cough medicine, the autopsy report indicated that her regime of clonidine, quetiapine, and divalproex had caused "damage to her heart and lungs from prolonged abuse of these prescription drugs, rather than one incident" (Wen, 2007).

Another case involved Destiny Hager, diagnosed with PBD at age 3 and prescribed two antipsychotics concurrently: quetiapine, 600 mg/day; and ziprasidone, unspecified dose. He died of fecal impaction (Carpenter, 2009).

A 2008 cover story of *Newsweek* was of "Max," a 10-year-old diagnosed and medicated around his second birthday. He was treated with 38 psychiatric drugs over the next 8 years (Carmichael, 2008). The *New York Times* recently highlighted the case of Kyle Warren, misdiagnosed with autism and PBD and treated with polypharmacy that commenced with an antipsychotic at 18 months of age. He experienced significant weight gain and loss of motivation (Wilson, 2010).

PARADIGM SHIFT FROM "BRAINLESS PSYCHIATRY" TO "MINDLESS PSYCHIATRY"

These cases signal a profound shift in the conceptualization and management of childhood emotional and behavioral problems. Such changes in practice imply a shift in the paradigm under which psychiatry is practiced. Kuhn (1962) proposed that science always proceeds in a social and historical context. The prevailing paradigm governs what is considered for study and treatment and what is not. Under the influence of a paradigm, even research of high intellect, internal consistency, and technical quality can lead to false conclusions.

Eisenberg (1986), head of the American Psychiatric Association's section on child and adolescent psychiatry, coined the terms *brainless psychiatry* and *mindless psychiatry*. These describe the poles of the pendulum swing from the pre-*DSM–III* (*Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed.) excesses of speculative psychoanalysis, overly zealous family therapy, and the anti-psychiatry movement to the excessive biological reductionism of the past two decades.

The *DSM–III*, published in 1980, was a key turning point, and the paradigm shift was under way by January 1990 when President George H. Bush declared the "decade of the brain." Since then there have been significant advances in neuroimaging, neurochemistry, and genomics. However, *Homo sapiens* evolved as a social species, and the biopsychosocial model remains a more philosophically robust basis for the health sciences (Borrell-Carrió, Suchman, & Epstein, 2004).

Beginning two decades ago, there have been warning voices about biomedical reductionism. Silove (1990), in the *Australian and New Zealand Journal of Psychiatry*, quoted Eisenberg with his reference to mindless psychiatry and stated,

> Australian psychiatry should consider the recent ideological shift in the USA to an extreme biological model of mental disorders . . . the field is at risk of being overwhelmed by a reductionist 'biologism' which assumes an organic causation for all abnormal human behaviour. (p. 461)

In 1989, Lipowski stated, "After a period marked by one-sided emphasis on psychodynamic and social issues, or what could be called 'brainless' psychiatry . . . we are witnessing an opposite trend towards extreme biologism or 'mindless' psychiatry" (p. 249). Tasman (1999) noted that economic forces have diminished psychodynamic training in the United States to the extent that "many fear we are in danger of training a generation of psychiatrists and physicians who lack . . . a framework for understanding mental functioning from a psychodynamic perspective" (p. 189). Boyce (2006), in an address to the Royal Australian and New Zealand College of Psychiatrists, blamed the "dumbing down" of psychiatry on "increased service demand, the deification of *DSM*, the influence of the pharmaceutical industry, a misunderstanding of evidence-based medicine (EBM), managerialism and the influence of consumerism" (p. 4). Commenting further on this paradigm shift, Scull (2010) noted, "A simplistic biological reductionism (has) increasingly ruled the psychiatric roost. Patients and their families learned to attribute mental illness to faulty brain biochemistry. . . . It was biobabble as deeply misleading and unscientific as the psychobabble it replaced" (p. 1247).

It appears to us that the common application of the PBD diagnosis reflects research and clinical practice that, consistent with the prevailing paradigm, underutilizes psychodynamics, family dynamics, attachment, trauma, and context. Frances (2010), the former *DSM–IV* task force chair, has gone so far as to critique PBD as a "fad diagnosis" of "epidemic" proportions.

Nonetheless, anecdotally it has been difficult for critics of PBD to publish in the psychiatric literature. In an era in which quantitative research is held in higher regard than qualitative research, 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.

One published exception in *JAACAP* was a commentary by McClellan (2005) to the Treatment Guidelines. McClellan bluntly stated, "Labelling tantrums as a major mental illness lacks face validity and undermines credibility in our profession" (p. 238). He also stressed the traditional basics of child psychiatry: "The developmental and family systemic context of children's moods and behavior reflect complex problems interwoven with temperament, attachment, parent-child relationships, cognition and other moderating/mediating factors including trauma" (p. 237). He implied that this sophisticated biopsychosocial paradigm is lacking in the PBD literature.

NOT EVERYTHING THAT COUNTS CAN BE COUNTED

One aspect of this paradigm shift has been an emphasis on structured interviews and rating scales, which are necessary in research. However, this comes at the expense of introspection and reflection about the presenting phenomenology of patients in their life narrative and context. Carlson (1998), despite being among the first to raise the issue of pre-pubertal mania, critiqued the checklist approach to diagnosis in PBD research. Carlson and Meyer (2006) noted, "The diagnosis of bipolar disorder is often made by mindlessly applying criteria . . . without understanding developmental history and context" (p. 963) and went on to propose "that bipolar research could benefit from a developmental psychopathology approach" (p. 963).

It can be argued that the extensive PBD research literature reflects a current biomedical reductionist and taxonomic approach to the phenomenology of children's and teenagers' behavior. But even in physics the quantitative approach is not everything. Einstein, whose ideas came more from intuition than calculation, hung a plaque in his office at Princeton University that stated "Not everything that counts can be counted, and not everything that can be counted, counts" ("Albert Einstein," 2008).

Biederman et al. (1995) have used subscales of the Child Behavior Checklist (CBCL) to define broad phenotype PBD or juvenile bipolar disorder (JBD)—hence "CBCL-JBD." However, a 10-year follow-up of prepubertal children diagnosed by the CBCL-JBD was found to lack predictive validity into adolescence for bipolar disorder (Halperin, Rucklidge, Powers, Miller, & Newcorn, 2011). A diagnostic checklist from "The Bipolar Child" and accessible online at www.jbrf.org also was found to lack predictive capacity for bipolar disorder in a study that used it retrospectively (Rucklidge, 2008).

NEGLECT OF TRAUMA AND ATTACHMENT FACTORS

Blader and Carlson (2007) found that a disproportionate number of Afro-American children received the PBD diagnosis. J. Harris (2005), a child psychiatrist working on a preteen inpatient unit in Boston, noted that

many children diagnosed with PBD were in foster care and had attachment trauma histories.

Edmund C. Levin, dealing with children in a residential program on polypharmacy cocktails typical for treating PBD, found over a 2-year period that milligrams of psychotropic medications could be reduced by 80% while aggressive incident reports fell by 100%. The reductions became possible by tapering medications while addressing trauma, attachment, milieu, and other factors. Most of the children at admission had a diagnosis of mood disorder not otherwise specified with comorbid attention-deficit/hyperactivity disorder. None warranted those diagnoses at discharge. Developmental trauma disorder (DTD; van der Kolk & Courtois, 2005) was felt to better describe their presentations (Levin, 2009).

We are not advocating brainless psychiatry. Developmental trauma can predispose or precipitate those constitutionally vulnerable to major psychiatric disorders like schizophrenia and bipolar disorder into manifesting the illnesses, but the effects of trauma can also present as affective instability and other ego defenses that may superficially resemble psychotic or severe mood disorders. Dissociation as a defense against trauma can particularly lead to symptoms easily confused with hypomanic and psychotic states (Silberg & Dallam, 2009).

Biomedical research is leading 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, 2002). Attachment theory is a bedrock concept of child psychiatry and the wider field of developmental psychology. However, a search of the PBD literature for reference to attachment theory finds almost no mention of it (Parry, 2010). There also is little mention of trauma and abuse. The Washington University in St. Louis group, who proposed what has since been termed narrow phenotype PBD, found no cases of posttraumatic stress disorder (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 (Rucklidge, 2006) of narrow phenotype PBD that used the same diagnostic methodology. This study found that more than 50% had a history of trauma and 21% met criteria for lifetime PTSD (10% trauma exposure, 0% PTSD among controls). The Harvard/Massachusetts General Hospital group, who proposed what has since been termed broad phenotype PBD, referenced Wozniak et al. (1999) to hypothesize that PTSD occurs secondary to PBD (i.e., a child who develops PBD early in childhood may create stressful situations by misbehaving). That may then lead to the child's being traumatized.

Herman (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)

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 behaviors—particularly as such diagnoses 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 health providers, particularly pediatricians and psychiatrists, for whom writing a prescription may bestow a sense of action and assistance.

Although we find little coverage of these issues in the PBD research literature, academics have debated in the public media. Pavuluri (Carey, 2007b) enunciated the benefits of the diagnosis: "These are kids that have rage, anger, bubbling emotions that are just intolerable for them, and it is good that this is finally being recognized as part of a single disorder" (i.e., PBD). However, van der Kolk, a psychiatrist prominent in PTSD research, said, "The (PBD) diagnosis is made with no understanding of the context of their life." Carlson has added, "Bipolar is being over diagnosed 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)" (Carey, 2007a). Williams (2008) critiqued PBD from a systemic perspective and described a 10-year-old boy erroneously diagnosed with PBD who was concurrently on eight psychotropics.

"DIAGNOSTIC UPCODING" IN THE U.S. HEALTH SYSTEM

Thus far, PBD has been a diagnosis mainly confined to the United States. Illustrating this are differences at various child and adolescent psychiatry conferences. In 2009 at the American Academy of Child and Adolescent Psychiatry (AACAP) conference in Hawaii there were at least 40 presentations on PBD and a further half dozen in a session chaired by Carlson about severe mood dysregulation as an alternative description for broad phenotype PBD. In contrast, there were *zero* presentations on PBD at both the 2009 Australian and New Zealand Child and Adolescent Psychiatry (CAP) conference in New Zealand and the larger European Society of CAP conference in Hungary. Furthermore, the British National Institute for Health and Clinical Excellence (2006) guidelines on bipolar disorder specifically recommend against using the PBD diagnosis in clinical practice. A German survey of child psychiatrists (Meyer, Koßmann-Böhm, & Schlottke, 2004) found that only 8% had ever seen a pre-pubertal bipolar disorder case.

Why is this so? One reason may be that the United States is one of the few nations to allow direct-to-consumer advertising. Psychotropics and

bipolar disorder have featured prominently in such advertising (Healy, 2006). Although the global media and Internet allow practitioners and parents to hear of PBD, still the diagnosis has not erupted as in the United States. Aspects of the U.S. health system appear to induce diagnostic upcoding pressures that drive a higher rate of bipolar disorder diagnoses. Diagnosis upcoding occurs wherever medical practitioners are under pressure to give a diagnostic label in order to provide treatment and be reimbursed.

Parry, Furber, and Allison (2009) surveyed Australian and New Zealand child psychiatrists about PBD. The survey noted that 90% thought PBD was "over-diagnosed" in the United States, 6% were "unsure," and only 3.5% thought it was "under-diagnosed" or "appropriately diagnosed" by American colleagues. In discussion, U.S. colleagues noted how health insurers may demand a diagnosis like bipolar before providing reimbursement. Blader and Carlson (2007) postulated diagnosis upcoding as a reason for the increase in PBD. In light of such pressures, Eist (1999), former president of the American Psychiatric Association, called the U.S. managed care health system "corpricare," as the system primarily serves the profit interests of private insurers. In particular, corpricare has tended to disadvantage the provision of psychotherapies more so than pharmacotherapy.

In Australia, diagnosis upcoding has emerged with Asperger's disorder with children inappropriately labeled because the diagnosis confers educational and family financial welfare assistance (Basu, 2010). But because it is based on clinical need, Australia's universal single payer health system does not require diagnoses for reimbursement for therapy and thus does not encourage a PBD epidemic.

INFLUENCE OF THE PHARMACEUTICAL INDUSTRY

Carlson alluded to causes other than upcoding for the PBD epidemic (Carey, 2007b): "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." Scull (2010) noted that the rise of "biobabble" makes priceless "marketing copy" and that "drug money has come to dominate psychiatry. It underwrites psychiatric journals and psychiatric conferences (where the omnipresence of pharmaceutical loot startles the naive outsider)" (p. 1247).

Investigations by Senator Charles Grassley, Chair of the Senate Finance Committee, question the relationships between the pharmaceutical industry and some academic psychiatry departments (Grassley, 2008). Internal industry documents indicate that companies seek a wider bipolar diagnosis to boost sales of antipsychotics. Analysis of these documents (Spielmans & Parry, 2010) leads to the view that much psychiatric literature and continuing medical education would be better described as promoting "marketing-based medicine" rather than "evidence-based medicine." This problem

has been described by former chief-editors of the *New England Journal of Medicine* in "Industry-Sponsored Clinical Research: A Broken System" (Angell, 2008) and of the *British Medical Journal* in "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies" (Smith, 2005).

Some pharmaceutical company documents (Spielmans & Parry, 2010) detail how, with the expiration of patents for many antidepressants in the past decade, new markets have been required to meet commercial needs. With most so-called second-generation antipsychotics (SGAs) still on patent, there has been interest in a wider bipolar diagnosis and a rebranding of SGAs as "mood stabilizers." Researchers with theories that converged with industry goals were more likely to get financial support. There is nothing intrinsically wrong with this if evidence-based medicine is truly adhered to. But such influence can promote positions that benefit industry financially.

The Grassley Committee, the *New York Times*, and the *Wall Street Journal* in their investigations focused upon some academic departments of child psychiatry. Documents of interest included the 2002 Annual Report "The Johnson and Johnson (J&J) Center for Pediatric Psychopathology at the Massachusetts General Hospital" (G. Harris & Carey, 2008), which stated,

> 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.

No one would fault the first two criteria; however, the third criterion is scientifically and ethically problematic. Janssen, a subsidiary of J&J, manufactures the SGA Risperdal. The report outlined the aims of the research:

> Because parents, patients and clinicians are exposed to a media that frequently questions the validity of childhood disorders, genetic and brain imaging studies are needed to show the validity of these disorders as brain disorders that respond to medication. . . . Without such data, many clinicians question the wisdom of aggressively treating children with medications, especially those like neuroleptics.

Mental health professionals should be familiar with systemic thinking that includes the biopsychosocial model. But it is not just the biopsychosocial factors acting upon the child and his or her family that need to be considered; indeed, the societal pressures that act upon psychiatry and mental health services also need to be considered. The pharmaceutical industry spends vast sums of money on marketing, research, and continuing medical education, and furthermore economic pressures place pharmaceutical

companies in fierce competition. In this context, the words of the chief executive officer of Eli Lilly, the manufacturer of Zyprexa, as written in an internal e-mail, reveal pressures to find markets in the pediatric age group: "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" (Berenson, 2008).

There has been growing awareness within the medical profession that liaisons with the pharmaceutical industry can be fraught with ethical dilemmas. As an editorial in the *American Journal of Psychiatry* with 26 signatories put it, "The interacting system of industry-supported clinical trials, advisory boards, and speakers' bureaus not always, but nonetheless too often, has resulted in conflicts of interest that have demeaned both psychiatry and the pharmaceutical industry" (Freedman et al., 2009, p. 275). Healy and LeNoury (2007) considered that as industry and others gain from the diagnosis, PBD can even be likened to a case of Munchausen's by proxy.

THE *DSM–III* AND *–IV* HAVE UNDERSTATED ATTACHMENT, TRAUMA, AND CONTEXT

Wittgenstein proposed that language and concepts affect perception (i.e., what is in our vocabulary we see; what is not can easily remain invisible). In psychiatric nosology, Scull (2010) pointed to the *DSM–III*, saying the "revolution" came in the form of an "anti-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" (p. 1247). Lane (2007) interviewed several on the *DSM–III* task force to conclude that a political agenda to depose psychoanalysis from its perch atop psychiatry's power structure drove the "atheoretical model" of the *DSM–III*. Despite significant advances in the attachment theory and traumatology research literature, both the *DSM–III* and *DSM–IV* have generally not incorporated this work. Silberg and Dallam (2009), focusing on dissociation in children and its association with disorganized attachment, relational stress, and trauma, noted 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 problem for psychiatric nosology is that diagnoses, including PBD within the bipolar disorder not otherwise specified rubric, lack relational context and suffer from reification and oversimplification (Dignam, Parry, & Berk, 2010; Parry, 2009).

Neuroimaging of children with disorganized attachment and trauma histories has revealed impaired right prefrontal cortex control over a hyperactive right amygdala. This can be explained in terms of the function of these structures in attachment relationships and for survival in the face of threat

(Schore, 2002). Neuroimaging of children diagnosed with PBD (DelBello, 2009; Pavuluri, 2009; Pavuluri, Passarotti, Harral, & Sweeney, 2009) found essentially the same findings but made no reference to attachment and trauma factors. As it specifically deals with attachment issues, DTD can be proposed as a more accurate descriptor for many children diagnosed with PBD (Levin, 2009). However, DTD is not officially within the *DSM–IV*. Thus, in the PBD neuroimaging research attention-deficit/hyperactivity disorder and PBD receive consideration, but DTD and attachment and contextual factors do not appear to.

IATROGENIC DISASTER?

Hyman, former director of the National Institute of Mental Health, has said, "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" (Groopman, 2007, p. 31). Elias (2006) reported, "Between 2000 and 2004 there were at least 45 deaths of kids where the 'primary suspect' was an atypical (antipsychotic) and more than 1,300 reports of other serious side effects." G. Harris, Carey, and Roberts (2007) reported, "In 2006 alone the [Food and Drug Administration] 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.'" Harris (2008) also reported that from "1993 through the first three months of 2008, 1,207 children given Risperdal suffered serious problems, including 31 who died." This investigative journalism used similar research methodology (personal communication, G. Harris with P. I. Parry, 2008) as academic research by Moore, Cohen, and Furberg (2007; personal communication, Moore with P. I. Parry, 2008), which found that atypical antipsychotics figure highly as a "primary cause" of death in all age groups on the Food and Drug Administration database.

Metabolic adverse effects are a concern with SGAs. In addition, although SGAs are supposedly low in extrapyramidal side effects, 430 children in foster care in the state of Texas in 2004 "were prescribed antidyskinetics drugs to control side effects from antipsychotics" (Strayhorn, 2006, p. 77). The academic literature (Wonodi et al., 2007) adds concern with a finding of a 6% rate of tardive dyskinesia in a cohort of 5- to 18-year-olds on SGAs for over 6 months. Zito et al. (2008) have drawn further academic attention to the harms of polypharmacy for Texas foster children.

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.

PENDULUM SWINGING BACK FROM PBD AND MINDLESS PSYCHIATRY

There are signs that psychiatry's paradigmatic pendulum may be swinging back from the mindless extremity of its arc. A 2-day workshop (Parens & Johnson, 2010) on controversies in PBD attended by some leading figures in child psychiatry concluded that "the bipolar label may fit poorly many of the children who have received it over the last decade" (p. 20) and highlighted the importance of a child's social "context." The workshop also pointed to problems of diagnostic upcoding: "It is a deeply regrettable feature of our current mental health and educational systems that some *DSM* diagnoses are better than others at getting children and families access to the care and services they so desperately need." The 2010 AACAP meeting included two symposia on PBD (AACAP, 2010a, 2010b), both questioning the diagnosis in many cases and highlighting research on contextual factors in affect regulation. Finally, one sign of change coming from the highest levels of the AACAP is that a September 2, 2010, *New York Times* article on Kyle Warren (Wilson, 2010) was e-mailed to all members of the AACAP by the president, Larry Greenhill. Professor Greenhill requested that AACAP members "please take a moment to read the article and watch the (associated) video." We would like to request the same of our readers.

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8

Paediatric Bipolar Disorder – Are Attachment and Trauma Factors Considered?

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1. Introduction

1.1 Debate over the boundaries of bipolar disorder

Significant debate and controversy surrounds the boundaries of Bipolar Disorder (BD). Proponents of a broader category for BD within psychiatric nosology (e.g. Akiskal, 2007) argue that more limited episodes of mood instability in both time and severity belong on a broader bipolar spectrum. Others (e.g. Paris, 2009) contend that hypomanic symptoms that fail to meet full DSM-IV or ICD-10 criteria for time or severity for BD-I and some BD-II disorders are more likely to represent reactive affective states related to environmental and relational stressors and/or personality traits or disorders. A widening of what constitutes BD beyond traditional concepts of manic-depressive illness has been related to historical and social factors impacting on psychiatric nosology (Healy, 2010).

In this context probably the most intense controversy has been over the way the borders of BD have been extended into childhood. Paediatric Bipolar Disorder (PBD), synonymous with "Juvenile Bipolar Disorder", has been described in an editorial (Ghaemi & Martin, 2007) in the *American Journal of Psychiatry* as "notoriously controversial, with the epicentre of the debate being whether the condition can be diagnosed in pre-pubertal children at all."

1.2 Historical perspective on PBD

1.2.1 Pre-1995 perspectives

In antiquity the term "mania" historically was applied to any state of frenzied madness or marked behavioural dyscontrol and, as Healy (Healy, 2008 p.7) illustrates, the manic states described by Hippocrates were essentially states of delirium accompanied by fever. According to Healy (2008, p.56) mania was not described in the context of manic-depressive illness until the mid 19th century by Baillarger in France and it was not until Kraepelin at the dawn of the 20th century that the term gained its widespread modern psychiatric usage.

Kraepelin noted amongst his 900 cases of manic-depressive psychosis that the disorder could have onset in adolescence but cases with onset prior to age 10 were sporadic with a rate of 0.4% (Silva et al., 1999). Traditionally BD has been viewed as having its onset in late adolescence to young adulthood. Rare sporadic pre-pubertal cases were described, but it wasn't until the 1980s that articles appeared raising the question that childhood onset cases

of BD may present atypically and could be being missed (Carlson, 1984). However clinical practice did not alter until after the appearance of a series of articles in the mid 1990s.

1.2.2 Post-1995: The "narrow" and "broad" PBD phenotypes

Two articles published in 1995 sought to redefine mania and BD as presenting in atypical but reliably measurable ways in children and adolescents. Researchers at Washington University in St Louis (WUSL) characterised mania in children as presenting with prolonged episodes of "ultradian" (several times per day) cycling of mood episodes (Geller et al., 1995), meanwhile a group from the Massachusetts General Hospital affiliated with Harvard (MGH/Harvard) (Wozniak et al., 1995) characterised mania in children as presenting with chronic irritability generally without distinct time limited mood episodes.

The *Journal of the American Academy of Child and Adolescent Psychiatry* has given PBD prominence in major reviews (Geller & Luby, 1997; Pavuluri et al., 2005; Kowatch et al., 2005; Liu et al., 2011) and a report on the National Institute of Mental Health (NIMH) "research roundtable on pre-pubertal bipolar disorder" (Nottelman, 2001). The NIMH research roundtable defined the two subtypes as "narrow phenotype" (WUSL) and "broad phenotype" (MGH/Harvard).

1.2.3 Rise in diagnostic rates of PBD

Following this academic lead the number of children and adolescents diagnosed with PBD in the USA skyrocketed. Community rates of BD diagnosis in the paediatric range increased 4,000% from 1994-5 to 2002-3 (Moreno et al., 2007) and PBD became the most common diagnosis in US preadolescent psychiatric inpatient units by 2004 (Blader & Carlson, 2006).

Blader and Carlson cited "diagnostic upcoding" as a major driving force for the increased rate of PBD diagnosis. "Diagnostic upcoding" occurs when factors extraneous to the patient's condition provide benefit for a particular diagnosis. These factors mainly involve the way health insurers fund health care based on diagnosis rather than clinical need. Thus a child with ADHD and Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) may be having serious problems relating to his family and school and need an inpatient evaluation, but the inpatient evaluation might only be funded if there is a diagnosis of BD. There has been less diagnosing of PBD outside the USA (Parry et al., 2009), perhaps because most other developed countries do not link mental health care so directly to DSM diagnoses.

The epidemiology of PBD is worthy of further study in itself as vastly differing rates of diagnosis have been found for mainly cross-sectional and retrospective recall studies. The diagnostic rate depends greatly on the criteria used by the researchers no matter where the studies are done (Van Meter et al., 2011) and thus reflects differing viewpoints and does little to assist resolution of the controversy. However a retrospective recall study of adults with BD reflected the international divergence: 2% of Dutch and German subjects reported pre-teen onset, whilst 22% of the USA cohort reported pre-teen onset (Post et al., 2008).

1.2.4 "Severe mood dysregulation" (SMD)

Follow-up studies of youth diagnosed with "broad phenotype" PBD have shown they are no more likely to progress to adult BD than the general population. This has led to a

renaming of this group as exhibiting "Severe Mood Dysregulation" (SMD) (Brotman et al., 2006; Dickstein et al., 2006; Stringaris, 2009 & 2011; Leibenluft, 2011).

1.3 A controversial diagnosis

The validity of PBD has been subject to vigorous debate in the literature and media (Parry & Allison, 2008) and described as a "fad diagnosis" in "epidemic" proportions by the head of the former DSM-IV task force (Frances, 2010). Psychiatrists have published books for parents both for (e.g. Papolos & Papolos, 2000; McDonnell & Wozniak, 2008) and against (Kaplan, 2011) the diagnosis. Kaplan argues diagnoses such as ADHD and ODD/CD often suffice without recourse to a "comorbid" PBD diagnosis.

The relationship of the pharmaceutical industry and psychiatry has been a focus of concern in recent years (Freedman et al., 2009). The PBD diagnosis has been a particular focus of this debate (Frances, 2010; Parry & Levin, 2011; Levin & Parry, 2011; Robbins et al., 2011).

The controversy surrounding PBD intensified following a much publicised and tragic medication related death of a 4 year old girl, Rebecca Riley, in Boston in 2006. In the wake of the tragedy, the Boston Globe reported that both Rebecca's 6 year old sister and 11 year old brother and both her parents were also diagnosed with PBD and BD. Also there was a litany of child protection notifications, including the battering of her brother by their father and that her 13 year old half-sister had been removed by child protection services due to alleged sexual abuse also by Rebecca's father (Cramer, 2007). In the wake of the tragedy vigorous debate about PBD amongst researchers and clinicians spilled into the public media. Van der Kolk, a Harvard professor prominent in traumatology research, was quoted saying: "the (PBD) diagnosis is made with no understanding of the context of their life" (Carey, 2007).

1.4 Alternative perspective: Attachment insecurity and developmental trauma

Thus one of the main critiques of the construct of PBD is that it has arisen from and compounded a neglect in psychiatric nosology of attachment insecurity and developmental trauma in the lives of children and adolescents (McClellan, 2005; Harris, 2005; Carlson & Meyer, 2006; Parens & Johnston, 2010; Parry & Levin, 2011).

To date there has not been any systematic literature review to test whether in fact this is the case. This chapter therefore explores whether developmental contextual factors have been neglected, through a systematic literature review of the presence of attachment theory and developmental trauma and maltreatment concepts in the PBD literature.

2. Methods

A systematic review of the literature was conducted using the Scopus academic search engine. Scopus allows for searches for specific words within large numbers of selected articles, which aids this type of literature review. Searches can be in various fields such as title, abstract and/or keywords. In particular an "All Fields" search with Scopus should detect a word when it is in the article's title, keywords, abstract and list of citations/references titles. The search covered the period from January 1995 to June 2010.

2.1 Defining a body of PBD literature

A body of PBD literature was defined by 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 since 1995 to 15 June 2010. This gave rise to 7,257 articles, though with low specificity for PBD articles. In Scopus an "All Fields" search detects a word in the article's list of citations as well as in title, keywords, and abstract. From the 7,257 articles an "All Fields" search for the word "attachment" found 165 articles of which 15 were PBD oriented. Full texts of these 15 articles were examined for context of the word "attachment".

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 1,113 publications. Perusal indicated high specificity to articles relating to PBD. 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.

2.1.1 PBD literature from "narrow phenotype" and "broad phenotype" researchers

From the PBD literature of 1,113 articles, two subsets of literature were defined by affiliation with the two academic child psychiatry departments that first promoted PBD: WUSL and MGH/Harvard. 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 should give some important indication as to the question of incorporation or otherwise of attachment theory and trauma concepts. 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 of these 201 publications were downloaded and manually searched for the terms – *attachment, trauma, PTSD*, *maltreatment*, *abuse*, and *neglect*. Only 3 articles were accessible by just abstract and citation list.

2.1.2 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. To aid specificity the above terms were searched in "Title" field only, to give a sample of 746 publications.

This "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*"]. Specific terms such as these were used to define publications that specifically referred to PBD rather than publications relating to offspring of adults with bipolar disorder. Only 8 articles were found.

3. Results

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" search. With overlap this amounted to 84 publications in total (Figure 1).

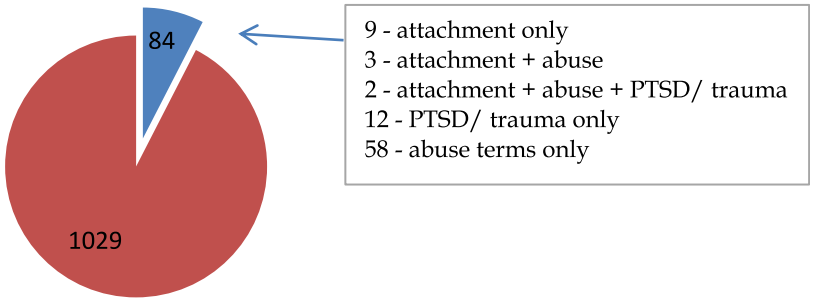

Fig. 1. Attachment and maltreatment/trauma terms in the PBD literature.

3.2 Fifteen PBD articles mentioning "attachment"

10 of the 14 articles that found "attachment" in the "all fields" search were PBD oriented, 4 related to (non-PBD) offspring of bipolar parents' studies. A further 5 articles were found from the less specific list of 7,257 articles. Thus 15 full-text articles were examined and the word "attachment" was used in the following contexts:

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 et al., 2006) accepted the validity of PBD phenotypes but promoted family therapy approaches. A review of PBD (Carlson & Meyer, 2006) was critical of over-diagnosis of PBD, noting that PBD research "would benefit from a developmental psychopathology perspective".

3.2.2 Attachment in text as minor theme (5 articles)

An American Academy of Child and Adolescent Psychiatry (AACAP) research forum on early-onset bipolar disorder (Carlson et al., 2009) contained a passage on contextual issues, maltreatment and family dysfunction. The article mentioned "insecure attachment" as a "risk factor for emotional dysregulation and externalizing disorders" among offspring of parents with bipolar disorder. This was one of the very few documents to use the term "maltreatment" and "insecure-attachment", though there was no specific mention of neglect or PTSD. The research forum also noted: "low socioeconomic status, stressful life events, cognitive style, negative hostile parenting as reflected in low maternal warmth, poor social supports, parent divorce and conflict and physical and sexual abuse have all been identified as risk factors for development of EOBP (early onset bipolar disorder)."

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 e.g. the importance of facial gaze in mother-infant dyads.

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. The offspring developed psychiatric disorders but not PBD.

McClure et al. (2002) expressed caution about the validity of PBD diagnoses and advocated for attachment perspectives in history taking and observations of child-family interactions.

A summary (Parens & Johnston, 2010) of a workshop on "controversies surrounding bipolar disorder in children" had "attachment" in a citation title and once in the text: "…workshop 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."

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 worsened course of bipolar disorder, discussed the ameliorating influences of psychotherapy and psychoeducation. "Attachment" was mentioned in the title of a reference (Insel) which was used in a 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."

A study (Meyer et al., 2006) of the Wisconsin Card Sorting Test in adolescent offspring of mothers with bipolar disorder had "attachment" in a citation title (Cicchetti) which was referenced in 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."

An article (Costello et al., 2002) that discussed abuse and parenting as minor themes had "attachment" in a citation title (Nachmias) which was used as a reference for: "evidence suggests that responsive caretakers may buffer the risk for depression and other forms of psychopathology". Another (Hirshfeld-Becker et al., 2003) had "attachment" in a citation title (Mannassis), which was referenced with others to say "some studies find an association between behavioral inhibition and anxiety disorders", and a fifth (Petti et al., 2004) had "attachment" in a citation title which was referenced in relation to a life events checklist that did not address attachment concepts, though social relationships were discussed.

3.2.4 "Parent-child relationship" as a keyword synonym for "attachment" (1 article)

The keyword "parent-child relationship" as a synonym for "attachment", appears to have led Scopus to choose an article (Schenkel et al., 2008) that stated: "Compared to controls, parent–child relationships in the PBD group were characterized by significantly less warmth, affection, and intimacy, and more quarreling and forceful punishment."

3.2.5 "Reactive Attachment Disorder" (1 article)

One article (Marchand et al., 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."

3.3 Full text searches of two academic centres prominent in PBD research

The above search for attachment, trauma and maltreatment terms was in "All Fields" so would not detect terms if in articles' text but not in title, abstract, keywords or citations. There were 201 articles from authors affiliated with WUSL (research centre to first propose "narrow phenotype" PBD) and MGH/Harvard (research centre to first propose "broad phenotype" PBD). These were full text searched.

3.3.1 PBD literature affiliated with WUSL

Eleven of 64 articles contained at least one of the searched terms except for "maltreatment".

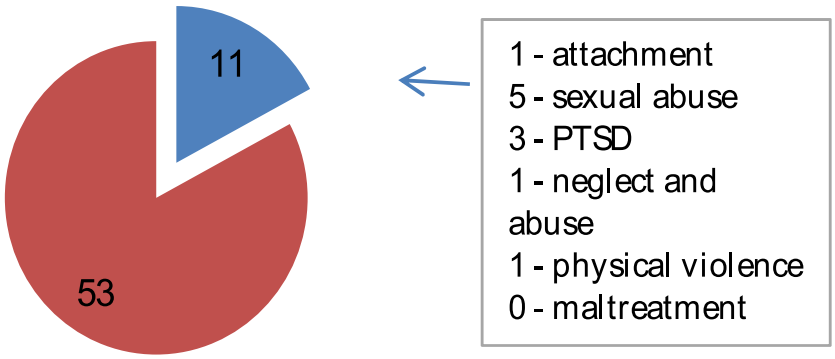

Fig. 2. Attachment and maltreatment/trauma terms in WUSL PBD literature.

As previously mentioned (Petti et al., 2004) contained "attachment" in a citation title. However though discussing the child subjects' social and family relationships, the article didn't address attachment per se in the text.

Five articles (Geller & Luby, 1997; Geller et al., 2000; Geller et al., 2002; Craney & Geller, 2003; Geller, Tillman, Badner, & Cook, 2005) contained the term "sexual abuse". These referred to "sexual abuse" as a differential diagnosis for "manic hypersexuality". They concluded that as only 1.1% in the cohort of 93 children with PEA-BP (prepubertal and early adolescent onset bipolar disorder) had "sexual abuse or overstimulation", whereas 43% (particularly the children who had hit puberty) had "manic hypersexuality" this "strongly supports hypersexuality as a symptom of mania" (Geller et al. 2002).

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 noted that with the cohort of 93 PEA-BP children there were significantly more adverse life events 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."

A study (Luby & Beldon, 2003), of 21 "Bipolar I" depressed preschoolers compared with 54 unipolar depressed preschoolers 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". 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". The authors did note a limitation of the study was: "Findings are also limited by sole reliance on parent report of symptom states, frequencies and duration".

One article (Craney et al., 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." 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 stated: "These data from the PEA-BP sample strongly point toward the need for research on non-pharmacological modalities".

3.3.2 PBD literature affiliated with MGH/Harvard

The Massachusetts General Hospital in Boston is affiliated with Harvard University and has been the main research centre proposing "broad phenotype" PBD. Of 137 articles, 23 contained one of the searched for terms somewhere in the full text.

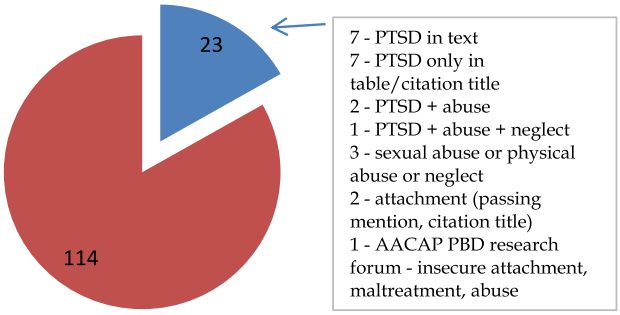

Fig. 3. Attachment and maltreatment/trauma terms in MGH/Harvard PBD literature.

The word "attachment" appears in 2 articles. One article (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."

The other (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 maniclike symptoms, they are not definitive as regards the treatment of bipolarity."

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 only mentioned PTSD in a diagnostic list or table: in a diagnostic list of anxiety disorders (Spencer et al., 1999; Hirschfeld-Becker et al., 2006); as a comorbid diagnosis with 14% of preschool and 10% of under age 10 PBD diagnosed children (Wilens et al., 2003); as 1 comorbid PTSD case in a cohort of 18 PBD diagnosed children (Moore et al., 2007a) and 2 of 32 PBD diagnosed children (Moore et al., 2007b) and another article on the same cohort listed 2 of 28 PBD diagnosed children comorbid for PTSD (Frazier et al., 2007). Another study (Harpold et al., 2005) found high rates of all anxiety disorders within a PBD cohort and that PTSD had the highest odds ratio of correlating with PBD and concluded "our results indicate that BPD (bipolar disorder) significantly and robustly increased the risk of a broad range of anxiety

disorders in youth." A recent study (Joshi & Wilens, 2009) also found high comorbidity rates with PBD. Wozniak (2003) did refer to PTSD in the text, 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)."

Three papers (Biederman et al., 2000; Biederman et al., 2003; Wozniak et al., 1999) that dealt with the issue of trauma and PTSD more directly in the text concluded that PBD precedes trauma and PTSD. A child with PBD is so disruptive that they create traumatic situations and family relationships that then impact traumatically upon them. Both Biederman et al. (2000, 2003) articles refer to the earlier Wozniak et al. (1999) study and 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)."

Wozniak et al. (1999) had 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…If confirmed, these results could help dispel the commonly held notion that mania like symptoms in youths represent a reaction to trauma."

The Wozniak et al. (1999) 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 – "our 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." They also noted they did not assess for PTSD at baseline: "the 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." 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.

The ages of the boys at the 4 year follow-up was 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. 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)." Despite this passage Wozniak et al. (1999) 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 nearly all 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 tended 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." Another article (Althoff et al., 2005) cautious in tone, stated: "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." Further caution was expressed in a study (Faraone et al., 2001) of girls with ADHD and bipolarity, noting: "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."

A recent article (Doyle et al., 2010) reported lack of specificity in the Child Behaviour Checklist for diagnosing JBD (Juvenile Bipolar Disorder – equivalent 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."

Six articles mentioned the term "abuse": physical and sexual abuse were listed in a trauma list (Wozniak et al., 1999); brief mention of sexual abuse as a differential to manic hypersexuality (Soutullo et al., 2009); physical and sexual abuse briefly mentioned in relation to PTSD (Steinbuchel et al., 2009); abuse 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); a study (Baldessarini et al., 2004) reported "no history of physical or sexual abuse was found

in any case" in a cohort of 82 PBD children (73% prepubertal with 74% having "onset of first symptoms" under age 3).

Another article (Bostic et al., 1997) mentioned infants being depressed in "abusive and neglectful situations". 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. The AACAP 2006 Research Forum (Carlson et al., 2009) had co-authors from the MGH/Harvard group and as above did mention maltreatment and abuse by name.

3.4 PBD terms in the attachment theory oriented literature

Just 8 papers were found by Scopus search for "attachment" in "All Fields" from a body of 746 articles. However on close examination not all these articles were strong on attachment theory based themes. The main focus for 7 of these was on anxiety and depression arising out of parent-child relationships. PBD was only a major theme in an editorial (Miklowitz & Cichetti, 2006) that was more in the context of the PBD literature (the journal, *Developmental Psychopathology*, issue was devoted to PBD) rather than attachment theory. It was possibly 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" or "maltreatment".

4. Comparison of neuroimaging reviews

Given that research in both developmental traumatology and amongst PBD investigators has focussed on neuroimaging in recent years, a comparison (but in this case not a systematic review) of neuroimaging reviews from both the PBD literature and attachment/trauma literature is of interest.

Schore 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. However both books focus on ROPFC dysfunction as primarily relating to impaired modulation of subcortical limbic structures and manifesting as affect dysregulation and behavioural impulsivity relating to disorders of attachment and trauma, disruptive behaviour disorders and personality disorders. The terms "bipolar", "mania/c" or "hypomania/c" do not occur in the review article.

A recent review (McCrory et al., 2011) of the neurobiological, genetic and epigenetic factors associated with childhood maltreatment also reports amygdala hyper-reactivity and reduced frontal cortical control of subcortical limbic structures. In particular fMRI studies of emotional processing of human faces in both adults and children revealed: "hyperactivity of the amygdale in response to negative facial affect." The review covers epigenetic changes that appear to underpin such neurobiological findings and the importance of secure-attachment to promote resiliency against such effects of maltreatment. Specifically it appears that "an early hostile environment contributes to stress-induced changes in the child's neurobiological systems that may be adaptive in the short term but which reap long term

costs." Additionally cognitive deficits, particularly deficits of working memory are correlated with maltreatment and institutionalization.

Interestingly the more recent PBD literature increasingly includes neuroimaging studies comparing PBD diagnosed cohorts with, for example, normal controls (e.g. Pavuluri et al., 2009a). None of the terms for attachment, PTSD or maltreatment/abuse appear in this article. Yet it describes similar findings concerning the right pre-frontal cortex and limbic system, including right amygdala reactivity and impaired right prefrontal cortical functioning, that the above reviews from an attachment and developmental trauma/maltreatment perspective describe.

5. Discussion

5.1 Attachment and trauma/maltreatment terms generally overlooked in PBD literature

A systematic review of the PBD literature via searching for the term "attachment" lends credence to critics' claims that the PBD literature in general does not address or consider attachment theory concepts. The almost complete absence of attachment theory concepts makes interpretation of trauma and maltreatment/abuse events in childhood problematic as there is evidence that attachment security/insecurity mediates the effects of trauma and abuse upon children (Cook et al., 2005). 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 WUSL report a virtual absence of PTSD in their cohort; researchers from MGH/Harvard suggest PTSD mainly arises secondary to PBD, though more recent publications from the group are more cautious.

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 New Zealand that found 29.2% reported sexual abuse on the same diagnostic instrument used in diagnosing the WUSL cohort, and over 50% of the New Zealand PBD sample had a trauma history compared with 10% of controls.

The MGH/Harvard group propose that PTSD where it does occur comorbidly with PBD arises secondary to PBD itself. However the main reference for this, a study (Wozniak et al., 1999) of 128 peripubertal boys with ADHD, of whom 14 had comorbid PBD, noted several limitations of their study including that it was of low power and that trauma and PTSD were not assessed at baseline. Nor from the article does it appear that early attachment histories had been taken in depth. Nonetheless if there was increased risk for experiencing trauma in the 4 year follow-up period for the boys with ADHD and a comorbid PBD diagnosis, an alternative hypothesis, not explored in the article, would be that the boys with ADHD and comorbid PBD at baseline were in fact exhibiting symptoms of earlier developmental trauma. Such earlier developmental trauma, mediated by psychodynamic, family dynamic, behavioural learning and other environmental contextual factors, could mean the 14 boys 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. More recent articles (Althoff et al., 2005; Steinbuchel et al., 2009; Doyle et al., 2010) from authors affiliated with MGH/Harvard are more open to the possibility of trauma factors causing or exacerbating symptoms, yet still conceptualise these symptoms in terms of PBD.

5.2 SMD articles also limit mention of attachment and trauma factors

As noted above, "broad phenotype" PBD has effectively been renamed "Severe Mood Dysregulation" (SMD) (Brotman et al., 2006; Dickstein et al., 2006; Stringaris, 2009 & 2011; Leibenluft, 2011). However a reading of these 5 papers suggests attachment and trauma related factors appear to be only a limited focus thus far, of research into SMD. Furthermore SMD is likely to feature in DSM-5 under the title: "Disruptive Mood Dysregulation Disorder" (DMDD). This proposed diagnosis has drawn some intense criticism, particularly from Frances, head of the former DSM-IV task force, who has described DMDD as one of the "worst ideas" for a new DSM diagnosis (Frances, 2011). Frances also notes that DMDD has likely been accepted as "a lesser evil replacement for childhood bipolar disorder—less stigmatizing and less likely to result in reflex long term antipsychotic use." But he suggests:

> "DMDD will capture a wildly heterogeneous and diagnostically meaningless grab bag of difficult to handle kids. Some will be temperamental and irritable, but essentially normal and just going through a developmental stage they will eventually outgrow without a stigmatizing diagnosis and a harmful treatment. Others will have conduct or oppositional problems that gain nothing by being mislabelled as mood disorder. Yet others will have serious, but not yet clearly defined psychiatric disorders that require careful and patient monitoring before an accurate diagnosis can be made."

However attachment, developmental trauma and maltreatment are still not mentioned.

5.3 Attachment theory based literature fails to mention PBD

Some PBD authors (e.g. Biederman, 2003) have strongly argued that mania and bipolar disorder is not considered by researchers who come from a more traditional child psychopathology perspective. A search of the attachment theory based literature, as outlined above, does in fact suggest unawareness or dismissal of the concept of PBD. However in defence of attachment oriented studies, it could be argued that most work to date has been in infancy and early child development prior to the onset of typical DSM clinical syndromes, at least as classically defined. Much of the attachment and developmental traumatology literature is in psychology, general science and neuroscience journals, whereas the PBD literature is primarily in US based psychiatry journals. To some extent this supports the hypothesis that there are differing paradigms governing the way children with severe emotional and behavioural problems are assessed and diagnosed.

5.4 Neuroimaging: PBD or developmental trauma/maltreatment

The specific case of neuroimaging in PBD research and attachment-trauma oriented research is an example where similar findings in the attachment-trauma oriented literature appear to be interpreted differently by authors from the PBD literature, and without cross-referencing.

Neuroimaging of children with disorganized attachment and trauma histories has, amongst other findings, revealed impaired right prefrontal cortex control over a hyperactive right amygdala. This can be explained in terms of the function of these structures in attachment relationships and for survival in the face of threat (Schore, 2002a). Neuroimaging of children diagnosed with PBD (Pavuluri et al., 2009) found essentially the same findings but made no reference to attachment and trauma factors. When this very interesting data from a

technically sophisticated study was presented at the AACAP 2009 conference (Pavuluri, 2009), I and others asked during the presentation why the children could not simply have been labelled as "affect dysregulated" rather than as having bipolar disorder? The presenter agreed they could well have, but stated that if they were not described as suffering bipolar disorder then research funding would be unlikely. At the same conference similar neuroimaging findings delineated an ADHD cohort from a PBD cohort (Delbello, 2009). The research again appeared to have high technical quality, but once again it is possible that a-priori assumptions may have governed the scope of possible conclusions. When I asked during the presentation if PTSD or disorganized attachment had been considered in addition to ADHD and PBD, the presenter replied that they had not been investigated.

The rise of new and exciting technological developments in neuroimaging and epigenetics hopefully will help develop understanding of childhood developmental psychopathology. But accurate understanding is likely to only grow if a wide range of hypotheses are maintained and all contextual factors, both historical and current, in a child's life are considered. McCrory et al. (2011) in their recent review, whilst acknowledging the high likelihood of trauma preceding brain changes, advocate for this and state that longitudinal studies are needed that "allow changes in the child's environment and behavior to be measured alongside changes in brain structure and function…if we are to make even tentative inferences regarding causality."

5.5 Perspectives from different paradigms

It has been argued that science proceeds not just in terms of applying the scientific method, but within a historical and sociocultural context with implicit assumptions and belief systems that set the parameters of the research, in other words according to a prevailing paradigm (Kuhn, 1962). The prevailing paradigm governs what is considered for study and treatment and what is not. Thus even research of high intellect, internal consistency and technical quality can lead to false conclusions if the paradigm is too restrictive. Furthermore differing paradigms can co-occur and be operative in the same era.

Based on this systematic literature review plus a selective review of neuroimaging research, there does indeed appear to be a communication gulf between two different paradigmatic approaches in child & adolescent psychiatry and developmental psychopathology.

Developmental Trauma Disorder (DTD) (Van der Kolk & Courtois, 2005) is another proposed diagnosis for DSM-5. DTD has been proposed as a more accurate descriptor for many children diagnosed with PBD (Levin 2009). However DTD is not officially within the DSM-IV, whereas ADHD is and PBD has been given semi-official status under the rubric of BD-NOS (BD Not Otherwise Specified). The DSM-IV diagnoses are used to guide and constrain much of the funding for therapy and research, particularly in the USA. Thus in the neuroimaging research presented at the AACAP 2009 conference, ADHD and PBD receive consideration, but DTD and attachment and contextual factors seemingly did not.

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 consequently mainstream psychiatry has become too detached from attachment theory, psychoanalysis and traumatology and the progress made in these fields (Dignam et al., 2010).

These factors, in conjunction with "diagnostic upcoding" pressures, the influence of the pharmaceutical industry and a societal tendency to repress recognition of trauma have been argued as fuelling the rise in PBD diagnosis rates (Parry & Levin, 2011). Rather than existing in parallel, 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.

5.6 Signs of increasing attention to attachment and trauma factors

In 2005 the first "treatment guidelines" for PBD (Kowatch et al., 2005) did not mention attachment or trauma factors and focussed almost exclusively on pharmacotherapy algorithms in treatment for PBD, although there was an accompanying critical commentary (McClellan, 2005). In 2006, although still labelling the phenomenology as BD, the AACAP 2006 research forum (Carlson et al., 2009) did list a range of contextual environmental adversity factors as implicated in the aetiology of PBD. In 2007 an official AACAP "practice parameter" publication (AACAP, 2007) included authors who have published articles sceptical about PBD. This AACAP practice parameter combined both paradigmatic perspectives with quite differing views within the one document. It contained a section on the "diagnostic controversy" which, referencing work from both WUSL ("narrow-phenotype" PBD) and MGH/Harvard ("broad phenotype" PBD), noted that "although symptoms of early-onset bipolar disorder appear stable over time (Biederman et al., 2004b; Geller et al., 2004) [citations in original], juvenile mania has not yet been shown to progress into the classic adult disorder." The practice parameter also listed "psychotherapeutic interventions" as important in treatment and noted "dialectical-behavioural therapy may be helpful for youths with mood and behavioural dysregulation."

At the 2010 AACAP conference there were two symposia (AACAP, 2010a & 2010b) each with several papers highlighting contextual factors and stressing a more non-aetiological descriptor of "affect dysregulation" rather than using the bipolar or mania label for children with mood swings. Also in 2010, a report (Parens & Johnson, 2010) of a 2 day workshop, involving researchers in the field of PBD, records vigorous debate over the validity of the PBD diagnosis. Attachment and trauma are mentioned and paradigmatic aspects of the issue are also canvassed. Also as illustrated in the literature review above, more recent articles from researchers affiliated with MGH/Harvard have drawn attention to the need for more research into PTSD related factors.

In contrast a recent review and meta-analysis of pharmacotherapy in PBD (Liu et al., 2011) made no mention of psychotherapy, nor of psychosocial factors in diagnosis. The review noted limited efficacy of traditional mood stabilizers (Lithium and anticonvulsants) in PBD, whereas second generation antipsychotics (SGAs) had more efficacy and speculated "such results are consistent with the hypothesis that pediatric-onset bipolar disorder may represent a different subtype of bipolar disorder that could respond to different treatments than those observed in adult-onset cases." It has been often argued however that SGAs simply exert their effect via sedation (e.g. Ghaemi & Martin, 2007; Frances, 2010; Kaplan, 2011) and do not confirm a particular diagnosis as for example juvenile mania.

5.7 Implications for therapy

The debate about whether a child with severe emotional and behavioural problems has PBD, versus DTD or ADHD plus/or ODD or CD is far from academic. The choice of treatment, the risk of suffering side-effects, the child's perception of self, the family's perception of their child and the perception and behaviour of relevant others such as teachers are strongly influenced by the diagnostic label. The controversy over PBD has become impassioned because of such consequences.

Treatment guidelines (Kowatch, 2005; Liu et al., 2011) for PBD strongly promote use of psychotropic agents. PBD has been blamed for leading to an explosion, particularly in the USA, in the use of atypical antipsychotic agents and polypharmacy approaches for children (e.g. Frances, 2010; Parry & Levin, 2011; Robbins et al., 2011; Kaplan 2011).

5.8 Limitations

This systematic literature review relied on one academic search engine, Scopus, albeit one that aids this form of literature search. Defining a body of literature in a sensitive yet specific enough manner proved somewhat challenging. A full reading of all 7,257 publications would be needed to make the searches more thorough. Nonetheless the hypothesis being tested pertains to a broad trend over the past decade and a half within child and adolescent psychiatry, rather than specific researchers or scientific articles. In that sense the use of Scopus in this manner to examine broad trends can be justified. Furthermore it can be argued that full text searching the literature from two US child and adolescent academic centres most strongly associated with developing the PBD phenotypes should give a strong indication of how attachment, maltreatment and trauma factors are considered in the wider PBD literature. The systematic literature review covered the 15 ½ years to June 2010 and it is quite possible that more may have been written on attachment and trauma/maltreatment factors in the very recent PBD literature. However the PBD phenotypes have become entrenched in research and clinical practice, at least in the USA, during the time frame since the germinal articles in 1995.

6. Conclusion

Intense controversy over the validity of PBD remains despite a decade and a half of research into the postulated PBD phenotypes. A main criticism of the PBD constructs is that they fail to consider attachment theory and maltreatment and developmental trauma factors.

A systematic search of the PBD literature presented here found this to generally be the case. There was a virtual absence of consideration of attachment theory. Trauma and PTSD was described as likely secondary to pre-existing childhood mania by researchers associated with the "broad phenotype" PBD construct. Maltreatment factors were relatively absent in findings from cohorts in both "broad phenotype" and "narrow phenotype" PBD research. Furthermore attachment, maltreatment and trauma factors do not appear to be a focus of research that reconceptualises "broad phenotype" PBD as SMD.

A comparison of neuroimaging studies from attachment/developmental traumatology and PBD research shows remarkably similar findings interpreted quite differently. Two different paradigms appear operative within the field. Increased dialogue across these paradigmatic

perspectives is likely to help resolve the controversial nature of PBD. To quote Carlson & Meyer (2006), PBD research "would benefit from a developmental psychopathology perspective". This involves greater consideration of attachment insecurity and a child's psychodynamic defences against traumatic contextual factors.

7. Acknowledgment

The author is grateful to Gareth Furber for the figures, and to Stephen Allison, Jon Jureidini, David Healy, Anja Kriegeskotten and Joy Elford for comments on the manuscript.

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Pediatric News

MDedge

COMMENTARY

Diagnostic Labels and Kids: A Call for Context

Publish date: February 22, 2012

The proliferation of diagnostic labels within the DSM for childhood emotional and behavioral symptoms has become something of an alphabet soup. It can be argued that the atheoretical, decontextualized, symptom focused model of the DSM-III (IV, and now 5), while giving a reliable descriptive nomenclature, has moved child psychiatry away from its traditional biopsychosocial systemic and integrative model (Med. J. Australia 2009;191:674-6). The literature, different international emphases in conference themes, and discussion with colleagues suggest that this problem is more acute in the United States than elsewhere. But the problem affects child psychiatry globally. (The ICD-10, used in many other countries, considers contextual factors on "Z codes" but in many respects replicates the problems of informational reductionism inherent in the DSM-IV.)

By Dr. Peter I. Parry

The latest proposed label for the DSM-5 is disruptive mood dysregulation disorder (DMDD). This proposed diagnosis has a brief but interesting and controversial history. Earlier iterations of DMDD have been termed severe mood dysregulation (SMD) and temper dysregulation disorder with dysphoria (TDD). Published articles on these constructs have only appeared within the last 5 years.

The DSM-5 Childhood and Adolescent Disorders Work Group described its main justification for introducing DMDD as the "dramatic ... marked upsurge" in bipolar disorder diagnoses among children. Yet, pediatric bipolar disorder (PBD) remains mainly confined to the United States. Why? What explains what Dr. Derrick Silove, professor in the school of psychiatry, University of North South Wales, Randwick, Australia, described several years ago as an "extreme biological model of mental disorders" that seems to have pervaded our specialty in the United States? (Aust. N. Z. J. Psychiatry 1990;1190:461-3).

Early History of PBD

The diagnosis of PBD arose from two U.S. research centers in the mid-1990s. Researchers at Washington University in St. Louis proposed a "narrow phenotype" PBD, in which children had euphoric as well as irritable and sad moods, mainly manifesting as several "ultradian" mood episodes per day. In contrast, researchers at Harvard University described a "broad phenotype" PBD, where children present with chronic irritability. The diagnosis increased markedly in the United States, with a 4,000% increase documented between 1994-1995 and 2002-2003 (Arch. Gen. Psychiatry 2007;64:1032-9).

The criticism of PBD has been strident. Deaths and side effects from polypharmacy in very young children made headlines from 2006 onward. The former chairperson of the DSM-IV task force, Dr. Allen Frances, noted in one fairly recent article that PBD fell outside DSM-IV criteria and described it as a "fad diagnosis" in "epidemic" proportions.

DMDD was proposed mainly from the research of Dr. Ellen Leibenluft of the National Institute of Mental Health and the DSM-5 Work Group, as an alternative construct to "broad phenotype" PBD (Am. J. Psychiatry 2011;168:129-42). Subsequent longitudinal research showed that children with "broad phenotype" PBD/DMDD failed to progress to adult bipolar disorder. Controversy also continues over "narrow phenotype" PBD.

The draft criteria for DMDD stipulate "severe recurrent temper outbursts in response to common stressors ... grossly out of proportion in intensity or duration to the situation ... inconsistent with developmental level ... occurring three or more times per week." The mood between outbursts is "persistently negative (irritable, angry, and/or sad)." The outbursts

and/or mood must be present in at least two settings and the problem must have lasted for at least 12 months. The child must be aged 6-10 years.

Exclusion criteria include psychotic and mood disorder, pervasive developmental disorder, post-traumatic stress disorder, and separation anxiety disorder, as well as, it would seem, "narrow phenotype" PBD – as elevated expansive mood lasting more than 1 day is an exclusion criteria.

The diagnosis can be comorbid with the disruptive behavior disorders – attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD).

The DMDD diagnosis has been welcomed by some who see it as mitigating overdiagnosis of PBD and highlighting the emotional aspect of children with severe temper tantrums. However, it has been criticized by proponents of "broad phenotype" PBD, others who would prefer it as a subtype of ODD, and the parent advocacy organization Child and Adolescent Bipolar Foundation – whose director has expressed concerns that it would lead to parents being blamed for being "unable to control their bratty kids"(Science 2010;327;1192-3). Some see the DMDD diagnosis as the same beast with a different name.

Lukewarm Reception for DMDD

Dr. Frances has criticized DMDD as being little better than PBD – "another monster" that is "too risky to be included in the DSM-5, 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."

Pediatric News

MDedge

Diagnostic Labels and Kids: A Call for Context

Publish date: February 22, 2012

To a great extent, DMDD and PBD are problems created by managed health care systems within the United States, because ongoing care is restricted to a few diagnostic labels resulting in "diagnostic up-coding." Brief consultations and pharmacotherapy are reimbursed in preference to a more time-consuming holistic, biopsychosocial approach that includes the child's family and all contextual factors.

In contrast, the practice of child psychiatry in Australasia and Europe is less dependent on managed care restrictions and can incorporate the holistic model. PBD is rarely diagnosed in those parts of the world (Child and Adolesc. Mental Health 2009;14:140-7).

While doing research for this piece, I conducted a review of the SMD/TDD/DMDD literature. Forty-seven English-language articles failed to mention attachment and gave minimal attention to trauma, maltreatment, parenting, and family dynamics as etiologic factors. Interestingly, a single German and one French article did focus on those contextual factors.

The DSM itself has come under intense criticism as of late because of its "a-theoretical" symptom checklist approach. This comes at the cost of the core psychiatric skills of taking a thorough history and mental state examination of not only the child, but also the child's family and environment. One way in which the DSM-5 could improve the focus on contextual factors would be to expand reactive attachment disorder (RAD) or include another proposed diagnosis: that of developmental trauma disorder (DTD). Both RAD and DTD acknowledge that childhood emotional and behavioral problems usually don't occur in a vacuum. Meanwhile, the emergence of the DMDD diagnosis can be seen as a symptom of a deeper problem in psychiatric nosology.

Like many (48 professional organizations have signed the American Psychological Association's online petition to the DSM-5 as of this writing), I, as a clinician, am concerned about the overemphasis on often-simplistic labels that pretend to explain all. As I have argued before, we must not lose sight of the traditional child psychiatric skills of synthesizing a thorough family and developmental history with exploration of attachment, family dynamic, trauma/maltreatment, and temperamental factors (J. Trauma Dissociation 2012;13:51-68). Indeed, Dr. Frances was right when he said that inventing a new diagnosis to combat a bad one is not necessarily a good idea.

Dr. Parry is a child and adolescent psychiatrist, and a senior lecturer at Flinders University in South Australia. He has worked in inpatient and outpatient Child and Adolescent Mental Health Services in South Australia, Queensland, and Wales (the United Kingdom). He is a member of "Healthy Skepticism," an organization dedicated to "improving health by reducing harm from misleading drug promotion."

Appendix A21:
Allan, D, Parry, P & Purssey, R 2012 'BRIDGE study warrants critique', *Archives of General Psychiatry*, vol. 69, no. 6, pp.643-645.

Available online from the publisher:
http://doi.org/10.1001/archgenpsychiatry.2012.118

LETTERS TO THE EDITOR

On *Your Child Does NOT Have Bipolar Disorder*

To the Editor:

It is interesting that the book review of Kaplan's *Your Child Does NOT Have Bipolar Disorder* by Drs. 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). Despite PBD being defined by U.S. researchers in 1995, it has not gained general currency in clinical practice outside the United States. For example, in 2009, at the American Academy of Child and Adolescent Psychiatry meeting in Hawaii, there were more than 40 presentations on PBD, whereas at the Royal Australian and New Zealand College of Psychiatrists and Faculty of Child and Adolescent Psychiatry meeting in New Zealand and the European Society for Child and Adolescent Psychiatry meeting in Hungary, there were none.

I have attempted to explore this geographic difference within child psychiatry in invited posts on Dr. Kaplan's blog on the *Psychology Today* website.[3] I thus must declare this collaboration with the author, although his invitation postdated my review of his book for *Australasian Psychiatry*.

Williamson and Althoff appreciate some of Kaplan's book. They note Kaplan "rightly indicts the media and the pharmaceutical industry for their hubris and greed in marketing the bipolar diagnosis to desperate parents and criticizes the field for overselling the efficacy of pharmaceutical treatments." They say they want to refer "many, many parents" to a book that helps parents understand why their child does not have bipolar disorder. They agree with Kaplan when he demolishes broad-phenotype (chronically irritable) PBD. However, they take issue with Kaplan's skepticism of narrow-phenotype PBD in prepubertal children for "[failing] to mention . . . the growing consensus that some children do exhibit clear episodic bipolar affective disorder, in which *DSM-IV* criteria are . . . met." This "consensus" is not as widespread as the literature would suggest. In the original cohort followed to young adulthood by Geller et al.[4], few manifested classic adult bipolar disorder. Many clinicians, particularly outside the United States, still hold the traditional view that prepubertal bipolar disorder is exceedingly rare. Such views do not generate research data but are represented anecdotally in online commentaries and in surveys and clinical guidelines.

Williamson and Althoff criticize Kaplan's critique of the Course and Outcome in Bipolar Youth (COBY) study as "self-fulfilling prophecy" by comparing it with an outcome study of lung cancer, implying it is a naive argument, but there is a world of difference between emotional and behavioral symptoms based on questionnaires to families who believe their children have bipolar disorder and the measurable pathology of lung cancer. They fail to mention that Kaplan's critique of the Course and Outcome in Bipolar Youth study was based on reasoning as to why its results differed so dramatically from other major longitudinal studies that looked for bipolar disorder in children (pp. 43–46).[5]

Williamson and Althoff are inaccurate in saying Kaplan reduces all "severe aggression and dysregulation to a simple matter of 'ADHD and ODD' [attention-deficit/hyperactivity disorder and oppositional-defiant disorder]" and recommends only stimulants and behavioral modification to parents of severely dysregulated and aggressive children, because Kaplan does cautiously recommend antipsychotics in severe nonresponsive cases of aggression (p. 155–156).[5] The lack of discussion of disruptive mood dysregulation disorder (DMDD) perhaps reflects the timing of submission for publication, because moves to have DMDD incorporated in *DSM-V* are fairly recent. However, a revised edition should address DMDD.

Williamson and Althoff criticize Kaplan's adherence to *DSM-IV* criteria, but Kaplan is not alone in this regard. The British National Institute for Health and Clinical Excellence (NICE) guidelines advocate strict adherence to *DSM-IV* criteria in clinical practice and reserving PBD criteria for research only. The PBD epidemic in the United States might have been avoided with a similar policy. The *DSM-V* is not likely to give much succor to proponents of narrow-phenotype PBD if there are no separate bipolar disorder diagnostic criteria for children and adolescents, the not-otherwise-specified category is removed, and the 4-day length criterion for hypomania is retained.

My review's only reservation was Kaplan could have explored "the effects of maltreatment, developmental trauma and attachment disruption" more, but this is a problem with *DSM* diagnoses in general and particularly with the

PBD and DMDD (including neuroimaging) literature. The publisher's afterword in Kaplan's book did raise these issues.

Kaplan's book is much needed in the United States, where the public are inundated with numerous pro-PBD books.

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Disclosure: Dr. Parry has authored an invited post on the *Psychology Today* blog of Dr. Kaplan, the author of the book he had previously reviewed.

http://dx.doi.org/10.1016/j.jaac.2012.08.017

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To the Editor:

The Book Forum Assistant Editor, Laura Prager,[1] suggested that a reviewed book authored by Stuart Kaplan "seems to miss the mark"; I think it may be the reviewers who do. The review of *Your Child Does NOT Have Bipolar Disorder,* by Williamson and Althoff,[2] failed to address the serious problems of overmedication and the incorrect overdiagnosis of this disorder. These problems then fall on those of us who comprise the largest portion of the membership of the American Academy of Child and Adolescent Psychiatry, i.e., those of us who are clinicians in the frontline of treating young patients. My impression of Kaplan's work is that he appropriately challenges the notion that anger, inattention, and impulsiveness must always call for the writing of prescriptions for multiple "mood-stabilizing" medications under the guise of treating "bipolar disorder." These are often unneeded medications, many of which have potential severe acute side effects and as yet unknown long-term effects on youth.

I also was taken aback by what reads to me more as character assassination by a book review rather than a collegial challenge of Kaplan's thesis. I am not so intimately familiar with Kaplan's book that I wish to try to defend it from the many assertions made against it, but I do see the attributions made by the reviewers as not helpful to the discourse. To say that his ". . . first assumption [is] couched in what seems to have become a required homage to the criteria of Robins and Guze" seems unfair, as does the reviewers' rhetorically asking, "Furthermore, would Dr. Kaplan also assert, for example, that a prospective cohort study following a group of smokers will influence the outcome by making the participants more likely to develop lung cancer?" followed by their then asserting "Dr. Kaplan's claim is tantamount to saying that we can 'make' ourselves bipolar if exposed to powerful enough suggestion." He never says this in his book. Also, he does not suggest "that child psychiatrists and psychologists should bury their heads in the sand" or deny the existence of the diagnosis of pediatric bipolar disorder. He does argue strongly against the overuse of the diagnosis, which to me as a clinician is a much needed point to make. The review leaves me feeling the attributions made to him are disrespectful, a disservice to the field of child psychiatry, and dismissive of those of us who question what seems to be an iatrogenic epidemic.

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Disclosure: Dr. Levin reports no biomedical financial interests or potential conflicts of interest.

http://dx.doi.org/10.1016/j.jaac.2012.08.014

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Pediatric Bipolar Disorder (PBD) – a Skeptical Mainstream Non-US Perspective

I am grateful to Dr Fisher for inviting this skeptical non-US perspective on PBD. Although I practice in Australia I was invited onto the board by Dr Carlat after publishing research on pharmaceutical industry documents released post-litigation [Spielmans G, Parry P, 2010 http://link.springer.com/article/10.1007/s11673-010-9208-8]. I had become aware of the documents as I studied the PBD phenomenon in the USA.

Amongst these documents was evidence of pharmaceutical companies seeking broadened criteria for bipolar disorder [see documents at http://www.healthyskepticism.org/global/news/int/hsin2009-12]. Documents noted that patents for SSRI's were expiring, whereas most atypical antipsychotics were young in their patent lives. Increasing bipolar disorder diagnoses was key to maximizing sales for on-patent antipsychotics. As Frances, chair of the DSM-IV task force remarked: "New diagnoses in psychiatry can be far more dangerous than new drugs." [Frances A, 2012 http://www.nytimes.com/2012/05/12/opinion/break-up-the-psychiatric-monopoly.html?_r=0].

PBD had become the most common diagnosis in pre-pubertal children in US psychiatric inpatient units by 2004 [Blader JC, Carlson GA, 2007 http://www.sciencedirect.com/science/article/pii/S0006322306014466]. "The epidemic of childhood bipolar" (as later described by Frances [Frances A, 2010 http://www.psychiatrictimes.com/bipolar-disorder/content/article/10168/1551005]) was of interest to colleagues here in Australia when we became aware of it. Many US phenomena disseminate globally and we wondered if PBD would too.

PBD Generally Not Diagnosed Outside USA

Steve Allison and I published in *Australasian Psychiatry*: "Pre-pubertal paediatric bipolar disorder: a controversy from America" [Parry P, Allison S, 2008 http://www.ncbi.nlm.nih.gov/pubmed/18335361], that examined the rise of the "narrow" and "broad" PBD phenotypes from US researchers in the mid 1990's. We later surveyed the Royal Australian & New Zealand College of Psychiatrists" (RANZCP) faculty of CAP and found majority skepticism: only 3.5% thought our US colleagues were not overdiagnosing bipolar disorder, 90% thought they were overdiagnosing and 6% were unsure [Parry P, Furber G, Allison S, 2009 http://www.ingentaconnect.com/content/bpl/camh/2009/00000014/00000003/art00005].

It is true that if similar epidemiological methodology to US PBD researchers is used then similar rates of PBD can be found outside the USA [Van Meter AR, Moreira AL, Youngstrom EA, 2011 http://europepmc.org/abstract/MED/21672501/reload=0;jsessionid=IZgyTcaw9FaVOmF5Gct9.6]. There are PBD research centers in Europe, notably Spain, and in South America that have links with US researchers. But 17 years after the first publication in the USA about the postulated PBD phenotypes, PBD has not been accepted in mainstream clinical practice in other countries. A German survey of child psychiatrists [Meyer TD et al, 2004 http://onlinelibrary.wiley.com/doi/10.1111/j.1399-5618.2004.00131.x/abstract?deniedAccessCustomisedMessage=&userIsAuthenticated=false] gave even more conservative results than our ANZ survey and the British *National Institute for Health and Clinical Excellence* (NICE) 2006 guidelines on bipolar disorder [NICE, 2006 http://www.nice.org.uk/CG38] stipulated that the PBD phenotypes were for research and not for use in clinical practice. A more recent German survey of inpatient diagnoses found a slight rise in bipolar diagnoses in late adolescence but no rise under age 15. They noted the contrast with US data: "While Blader and Carlson reported …73 children and 204 adolescents per 100,000 …the rates in Germany …are 0.14 and 5.22 per 100,000." [Holtman M et al, 2010 http://onlinelibrary.wiley.com/doi/10.1111/j.1399-5618.2010.00794.x/full].

The international discrepancy in PBD diagnoses was reflected in 3 main CAP association meetings in 2009: at AACAP in Hawaii there were over 40 oral PBD presentations, whereas at both the RANZCP faculty of CAP meeting in New Zealand and the large European ESCAP meeting in Hungary there were none. At the IACAPAP World Congress of CAP this year in Paris there was a debate: "Paediatric bipolar disorder, severe mood dysregulation or what?" [IACAPAP, 2012 http://www.colloquium.eu/site/IMG/pdf/12IACAPAP-Debate-Pediatric_Bipolar_Disorder.pdf] where the widely discrepant international views were again apparent.

So Why the Discrepancy?

PBD in the USA has arisen during a time where: the biomedical paradigm is ascendant; quantitative data is valued over qualitative data with diagnoses based on structured interviews rather than multiple less structured sessions with children and families; the US health system encourages "diagnostic upcoding" based on DSM diagnoses which since DSM-III have mostly de-coupled from psychosocial contexts; the pharmaceutical industry has exerted an unhealthy influence in research, medical education and consumer awareness; and attachment and trauma factors are often overlooked [Parry P, Levin E. 2012 http://www.tandfonline.com/doi/pdf/10.1080/15299732.2011.597826].

"Not everything that counts can be counted…"

…and not everything that can be counted, counts." (Einstein). The use of structured interviews/rating scales for diagnosing PBD has been criticized [Carlson GA, http://www.sciencedirect.com/science/article/pii/S0165032798001797]. Kaplan gives a detailed critique in his book *Your Child Does NOT Have Bipolar Disorder* and on his *Psychology Today* blog of the same title [Kaplan S http://www.psychologytoday.com/blog/your-child-does-not-have-bipolar-disorder].

There is a bit of debate in the letters section of this month's *Journal of the American Academy of Child & Adolescent Psychiatry* over a critical book review of Kaplan's book [Williamson G, Althoff RR, 2012 http://www.jaacap.com/article/S0890-8567%2812%2900370-X/fulltext ; Parry PI, 2012 http://www.jaacap.com/article/S0890-8567%2812%2900642-9/fulltext]. Kaplan's book received wholly positive reviews in *Australasian Psychiatry* [Parry PI, 2012 http://apy.sagepub.com/content/19/5/446.full] and the *Journal of the Canadian Academy of Child & Adolescent Psychiatry* [Matheson K, Carrey NJ, 2012 http://www.cacap-acpea.org/uploads/documents//Book_Reviews_Aug_2012.pdf]. In their letter, Williamson & Althoff acknowledge that PBD is overdiagnosed and advocate for a more agnostic diagnostic stance on emotionally dysregulated children, but they still describe Kaplan's view that bipolar disorder is extremely rare prior to puberty as "extreme" [Williamson G, Althoff RR, 2012 http://www.jaacap.com/article/S0890-8567%2812%2900602-8/fulltext].

Beyond the USA the view that pre-pubertal mania is extremely rare to non-existent is mainstream. This view is rooted in attachment theory, psychodynamic theory, developmental psychology, family systems theory and developmental trauma research. It is borne out in long term family therapy, intensive parenting training, dyadic parent-child post-trauma therapies, and playtherapy. This is traditional clinical practice which finds biopsychosocial case formulations to be more informative than most DSM diagnostic labels.

Decontextualised symptom checklist approach since DSM-III

The late eminent US child psychiatrist Eisenberg coined the terms “brainless psychiatry” and “mindless psychiatry”. When psychoanalysis was overly dominant in the 1960s it was a “brainless” time in psychiatry, these days we practice in an era where the dominant biomedical paradigm is a “mindless” one [Eisenberg L, 1986 http://www.ncbi.nlm.nih.gov/pubmed/3535971]. According to a presidential address to the RANZCP, there has been a “dumbing down” of psychiatry and the biological reductionism since DSM-III takes much of the blame [Boyce P, 2006 http://www.ncbi.nlm.nih.gov/pubmed/16630189]. DSM diagnoses too often equate with presumed neurochemical imbalances and lead to first line or only line pharmacotherapy. Prominent US psychiatrists have argued that "reification of DSM-IV entities, to the point that they are considered to be equivalent to diseases, is more likely to obscure than to elucidate research findings" [Kupfer DJ, First MB, Regier DA, 2002 A research agenda for DSM-V, p xix http://books.google.com.au/books?id=6yXlYYls23MC&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false].

There is mounting opposition to the DSM model as evidenced by a petition [http://dsm5-reform.com/the-open-letter-to-dsm-5-task-force/] signed by over 14,000 mental health practitioners and 50 mental health professional associations.

PBD (and DMDD) Literature Overlooks Attachment and Trauma

I conducted a systematic literature review for concepts such as attachment theory, post-traumatic stress, child abuse, maltreatment and neglect in the PBD literature and found virtually nothing [Parry PI, 2012 http://www.intechopen.com/books/bipolar-disorder-a-portrait-of-a-complex-mood-disorder/paediatric-bipolar-disorder-are-attachment-and-trauma-factors-considered-]. The PBD literature focused on symptom clusters, rating scales, pharmacotherapy, genetics (though no clear answers) and neuroimaging (though no discernible reference to identical neuroimaging findings from the attachment-trauma literature). There was minimal mention of psychodynamic or family dynamic factors. A similar picture was evident in a brief review of the Severe Mood Dysregulation / Disruptive Mood Dysregulation Disorder literature [Parry PI, 2012 http://www.clinicalpsychiatrynews.com/views/commentaries/single-article/diagnostic-labels-and-kids-a-call-for-context/5783d363fe823984bafbef98b0ffaa75.html].

At IACAPAP in Paris this July Prof Biederman was asked if research involving parents of PBD children considered borderline personality disorder and he said no. I asked if his research had looked at attachment theory and was informed there was no time for such research.

Harris noted that developmental trauma/maltreatment was a factor for children erroneously diagnosed with PBD in a Boston inpatient unit [Harris J, 2005 http://ps.psychiatryonline.org/data/Journals/PSS/3642/529.pdf]. During my 5 years on an inpatient unit with a catchment of a whole Australian state, the youngest case of mania was aged 14. Colleagues since informed me of a 12 year old pubertal boy with definite mania and a 5 year old girl who presented as quite manic and this aroused interest as a possible true pre-pubertal case – until it was noticed her manic symptoms appeared *only* when her mother was present. I saw one possibly manic 7 year old boy but his manic-defense coping mechanisms completely resolved after disclosure of sexual abuse and jailing of the perpetrator.

Trauma denial has a long history. Freud theorized about infantile libido on the basis of incredulity over child sexual abuse disclosures by his Viennese female patients. Abuse, pathogenic family dynamics and attachment insecurity are frequent amongst stressed families. The desire for a shame-free biological explanation and medication fix can be high.

Levin describes how addressing underlying trauma, using Developmental Trauma Disorder rather than PBD as a diagnosis, and appropriate staff training in 2 therapeutic residential units was useful in reducing medication prescriptions by 80% and violent incidents by 100% over a 2 year period [Levin EC, 2009 http://www.ncbi.nlm.nih.gov/pubmed/19764849].

"Diagnostic Upcoding" and Australia's Variant on PBD is ASD

Blader and Carlson argued that "diagnostic upcoding" had driven the rise in PBD because the US health system demands more serious diagnoses in order to get treated. No other developed nation has this health system driver for bipolar disorder like the USA does.

Whilst Australia has avoided an epidemic of PBD, there is an overdiagnosis epidemic of Autistic Spectrum Disorders (ASD). Diagnostic upcoding factors include welfare payments to families of ASD children; our universal health system gives rebates to allied health practitioners for diagnosing ASD; and most Australian state education departments tend to only give special educational assistance for children with ASD or IQ under 70. Canada seems to have a similar issue [Thivierge J, 2008 http://thenadd.org/nadd-bulletin/archive/volume-xi/].

Influence of Pharmaceutical Industry

Much has been written elsewhere on this topic. I'd like to note just one personal experience: A PBD researcher at AACAP 2009 was asked in the session why not call the children "affect dysregulated" rather than "bipolar". The reply was frank: "if we don't call them 'bipolar', we won't get funding."

Final comment

Practising in Australia I've yet to see any pre-teen cases of mania, and neither have most CAP colleagues I know. However I accept that rare true bipolar cases can occur in pre-pubertal children, e.g. Carlson described a convincing case [Carlson GA, 2009 http://ajp.psychiatryonline.org/article.aspx?articleid=100448]. Again I thank Dr Fisher for allowing this skeptical perspective to be presented.

ORIGINAL ARTICLE

Psychotropic Marketing Practices and Problems

Implications for DSM-5

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Abstract: The descriptive diagnostic model since *DSM-III* has often led to "cookbook" diagnosis and assumptions of "chemical imbalance" for psychiatric disorders. Pharmaceutical companies have exploited this in their marketing. This includes promoting self-diagnosis with online checklists. Significant overprescribing of psychotropics has resulted. *DSM-5* will provide new disorders and broader diagnostic criteria that will likely exacerbate this. Most psychotropic prescribing is done by primary care physicians, who are problematically excluded from *DSM-5* field trials and are influenced by industry-funded key opinion leaders who may promote diagnosis of subthreshold cases. More lax criteria will increase diagnosis of subthreshold cases. Expansion of not otherwise specified (NOS) categories can be used to justify off-label promotion. Pediatric bipolar disorder, constructed within the bipolar disorder NOS category, became an "epidemic" in the United States, fuelled by diagnostic upcoding pressures. Disruptive mood dysregulation disorder may similarly cause overdiagnosis and excessive prescribing, as will other new disorders and lower diagnostic thresholds.

Key Words: *DSM-5*, psychotropic marketing, off-label promotion, key opinion leaders, self-diagnosis, NOS, pediatric bipolar disorder, disruptive mood dysregulation disorder.

(*J Nerv Ment Dis* 2012;200: 512–516)

A major theme of the current debate about the *DSM-5* is the potential for the diagnostic criteria to escalate inappropriate diagnosis and unnecessary, potentially harmful prescribing. This could occur both with proposed new disorders and with broadened criteria for existing disorders, which will be used by pharmaceutical companies to market profitable psychotropic drugs.

A major problem is the reification of descriptive *DSM* labels to equate to discrete pathological states of neurochemical dysfunction treatable with a pill (Boyce, 2006; Scull, 2010). The atheoretical descriptive model of *DSM-III* (American Psychiatric Association [APA], 1980) purposely decontextualized diagnoses from putative causative factors. This introduced reliability to diagnosis in research and practice but left valid understanding of symptoms in the real lives of subjects and patients to the clinical wisdom of researchers and clinicians. Unfortunately, however, a "checklist" approach to diagnosing soon became common and has been co-opted by the pharmaceutical industry.

The *DSM* effect operates at a society-wide paradigmatic level. Reification of *DSM* labels occurs in clinical practice, social discourse and public understanding, legal and insurance cases, schools, and in epidemiology and research. Too often lost is the full biopsychosocial systemic understanding of individual patients in their life context. Robert Spitzer, head of the *DSM-III* Task Force, in the foreword to Horwitz and Wakefield's (2007) *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow Into Depressive Disorder*, says that the arguments about context "has caused me to rethink my own position," and he continues:

> *the very success of the DSM and its descriptive criteria…has allowed the field of psychiatry to ignore some basic conceptual issues…the DSM criteria sets…specified the symptoms that must be present to justify a given diagnosis but ignored any reference to the context in which they developed. In so doing, they allowed normal responses to stressors to be characterized as symptoms of disorder. (p. viii)*

The pharmaceutical industry spends billions on research, continuing medical education (CME) and marketing, lobbying of health insurers and health bureaucracies, and direct-to-consumer advertising (DTCA). DTCA is increasingly available via the Internet beyond the two countries (United States and New Zealand) where it is legal. This economic might gives 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.

As Boyce (2006, p. 4) put it in a presidential address to the Royal Australian and New Zealand College of Psychiatrists:

> *The current paradigm seems to be that if a patient suffers from a specific DSM disorder, then there is a specific medication for this. If that medication does not work, try some other medication.*

Psychiatric drugs are widely and increasingly used, primarily in primary care settings. They generate huge profits, particularly "blockbusters" such as Prozac and Risperdal. Consequently, 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.

This is the philosophical backdrop to considering the psychotropic marketing implications of *DSM-5*. In this article, we discuss psychotropic drug prescribing, problematic marketing practices relevant to the *DSM-5*, and problematic diagnostic practices.

PSYCHOTROPIC PRESCRIBING

Most mental health treatment is provided in primary care settings (Wang et al., 2007). Therefore, most psychiatric drugs are prescribed by nonpsychiatrists. In the United States, primary care physicians (PCPs) prescribe most psychotropics (Mojtabai and Olfson,

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Editor's note: The proposed *DSM-5* criteria sets do not represent the final *DSM-5* criteria for the disorders.

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ISSN: 0022-3018/12/20006-0512
DOI: 10.1097/NMD.0b013e318257c6c7

2008). According to the US National Prescription Audit Plus Database of IMS', 59% of psychotropic prescribing from August 2006 to July 2007 was by PCPs, obstetrician-gynecologists, and pediatricians; 23% was by psychiatrists and addiction specialists; and 6% was by physician assistants and nurse practitioners (Mark et al., 2009). Pharmaceutical companies thus target PCPs in many marketing campaigns (Applbaum, 2009).

The prescribed psychotropic market is huge. A Medco (2011) study found that more than one in five insured US adults use at least one psychiatric medication, a 22% increase in a decade. Pediatric psychotropic prescribing has increased markedly, particularly in the United States (Cox et al., 2008; Olfson et al., 2006; Zito et al., 2008).

Up to 60% of drug prescriptions in the United States are off-label (*i.e.*, for diagnoses or age groups other than the approved indications) (Spetie and Arnold, 2007). Off-label pediatric prescribing of psychotropics has increased dramatically (Alexander et al., 2011; Lakhan and Hagger-Johnson, 2007).

Much psychotropic prescribing is rapid and routine. According to an ex-president of the American Psychiatric Association (APA):

> *"Brief consultations have become common in psychiatry," said Dr. Steven S. Sharfstein, a former president of the American Psychiatric Association and the president and chief executive of Sheppard Pratt Health System, Maryland's largest behavioral health system.*
>
> *"It's a practice that's very reminiscent of primary care," Dr. Sharfstein said. They check up on people; they pull out the prescription pad; they order tests."* (Harris, 2011)

There is evidence that doctors' prescribing is influenced by pharmaceutical industry marketing (Spurling et al., 2010), as would be expected given the massive expenditure on marketing and the claimed return on investment (Neslin, 2001). PCPs seem particularly influenced (Ward et al., 2008), partly because they are "largely reactive recipients" of drug information, and more reliant on the pharmaceutical industry (Prosser et al., 2003, p. 65).

DSM-5: NEW DISORDERS AS MARKETING OPPORTUNITIES

New disorders and broadened diagnostic criteria provide pharmaceutical companies with opportunities to develop new markets. Industry documents show that *DSM* criteria are often regarded as targets for new indications approved by the Food and Drug Administration (FDA) and other regulators (Applbaum, 2009, p. 198; Dickersin, 2008).

One current example of how the pharmaceutical industry is likely to capitalize on the inclusion of new diagnostic entities in *DSM-5* is premenstrual dysphoric disorder (PMDD), which was added to the *DSM-IV* (APA, 1994) appendix of disorders needing further study and is now proposed as an official *DSM-5* disorder. Its inclusion in the appendix as an example of Mood Disorder Not Otherwise Specified gave it enough status to spur the pharmaceutical industry to pursue a new indication. Currently, Sarafem (reformulated Prozac) and the contraceptive pill YAZ are marketed for treatment of PMDD (Ebeling, 2011). It is likely that approvals will be sought for other drugs if PMDD gains full *DSM-5* status.

Another proposed new disorder in *DSM-5* and likely target for a new drug indication is binge eating disorder (BED) (Moran, 2012). An FDA panel recently recommended approval of Qnexa, a combination of phentermine (an anorectic) and topiramate (an anticonvulsant), for treatment of obesity. Topiramate is currently being promoted as a treatment for binge eating (Reynolds, 2012). It seems likely that Qnexa will also be promoted for this purpose. FDA approval for Vyvanse for treatment of BED is already being sought (Tirrell, 2011).

PROBLEMATIC MARKETING PRACTICES

Much has been published about problematic practices in prescribed drug marketing (Angell, 2004; Elliot, 2010; Moynihan and Cassels, 2005), particularly in psychiatry (Angell, 2011; Scull, 2010). Problematic practices have been exposed by Senator Grassley's Congressional investigation of pharmaceutical industry payments to physicians (Carey and Harris, 2008) and in court cases. Some practices encourage inappropriate diagnosis as well as inappropriate prescribing.

Off-Label Promotion

The pharmaceutical industry has a track record of promoting off-label prescribing (Kravitz et al., 2005; Steinman et al., 2006). This is a meta-marketing strategy in which drug representatives, key opinion leaders (KOLs), and industry-funded CME play key roles.

Although doctors are allowed to prescribe for nonapproved indications, it is illegal for manufacturers to promote off-label prescribing. However, the authority of *DSM* diagnoses, including not otherwise specified (NOS) diagnoses, can provide justification for prescribing for nonapproved indications and opportunities for off-label promotion.

New indications are commonly sought for existing drugs (Chouinard, 2006), but regulatory approval is not always sought. Dickersin (2008) documented how Parke-Davis used an "indication strategy" (seeking FDA approval) for some indications for Neurontin but a "publication strategy" for other *DSM-IV* indications. A publication strategy involves funding trials for publication as part of a marketing campaign rather than for application to the FDA.

Key Opinion Leaders

The use of KOLs is a key marketing strategy (Moynihan and Cassels, 2005). KOLs are paid for participation in CME, clinical trials, advisory groups, and guideline development panels.

The value of KOLs, often prominent academics, is their blend of status and credibility. Specialists have considerable influence on PCPs' prescribing habits (Florentinus et al., 2009). CME is a key channel via which KOLs influence PCPs. Clinical practice guidelines are increasingly influential (Healy, 2012). Even without specific industry funding, guidelines are susceptible to industry influence (Sniderman et al., 2009).

The relevance of the *DSM* to KOLs and CME is via the decontextualized symptom-focused model of *DSM*, co-opted and exploited by the marketing power of the pharmaceutical industry, for example to imply that a "chemical imbalance" underlies psychiatric disorders (Pies, 2011). The NOS category gives ample room for expansion of disorders and prescribing into off-label territory, so KOLs who advocate expanding disorder boundaries via NOS categories are valuable to industry.

In the United States, KOLs who promoted pediatric bipolar disorder (PBD) under the bipolar disorder NOS rubric came under scrutiny for industry links (Levin and Parry, 2011). In Australia, prominent KOLs have promoted the controversial diagnosis and treatment of "psychosis risk syndrome" (proposed for inclusion in *DSM-5* under the name "attenuated psychosis syndrome"; Frances, 2011) and other risk syndromes (McGorry, 2010), including a "pluripotential risk syndrome" (McGorry et al., 2010). They have developed a clinical staging model to facilitate early and preemptive intervention (McGorry et al., 2006). Their work promotes diagnosis and treatment of cases that do not meet strict diagnostic criteria.

The more lax the criteria, the greater the number of subthreshold cases. Broad criteria increase the plausibility of diagnosis

based on minor symptoms, which makes it easier for KOLs to promote inappropriate diagnosis. The NOS categories, although useful for research, provide fertile ground for diagnostic inflation and overprescribing.

Disease Awareness Campaigns: Checklists for Self-Diagnosis

Pharmaceutical companies commonly use disease awareness campaigns and often include symptom checklists, an ideal mechanism for the promotion of self-diagnosis. Drug company Web sites commonly provide checklists for people to take to their doctor to discuss.

Ebeling (2011) used a case-study of PMDD to illustrate how self-diagnosis is used as "a marketing tool to construct a well-educated consumer who will demand medical diagnoses inline [sic] with a drug company's objectives" (p. 825). Ebeling noted that a member of the *DSM-IV* PMDD Work Group was involved in the development of a symptom checklist, the "YAZ Body Diary" for Bayer, the manufacturer of the contraceptive pill YAZ (drospirenone/ethinyl estradiol), which was marketed for treatment of PMDD.

Promotion of self-diagnosis by checklist allows more individuals to self-identify as having a disorder. It is an important mechanism by which lowered *DSM* diagnostic thresholds increase the pool of potential customers for those disorders.

PROBLEMATIC DIAGNOSTIC PRACTICES

Expansion of NOS Categories

Much of the concern voiced about draft *DSM-5* criteria focuses on the lowering of the diagnostic bar for several disorders. For example, a diagnosis of adult attention deficit hyperactivity disorder could be made with four criteria rather than six (APA, 2010a). In addition, as mentioned above, the NOS categories in *DSM-IV* permit diagnosis and treatment of subthreshold cases. Moreover, *DSM-5* is proposing to split *DSM-IV* NOS categories into two residual diagnoses with different names: Other Specified Disorder and Unspecified Disorder. For example, the Feeding and Eating Disorders section will replace Eating Disorder NOS with two diagnoses: Other Specified Feeding or Eating Disorder (OSFED) and Unspecified Feeding or Eating Disorder (UFED) (APA, 2010c). OSFED will contain "brief descriptions of several conditions of potential clinical significance [that] are provided so that that the problems of individuals with feeding or eating problems not meeting criteria for currently recognized disorders can be more appropriately described and categorized." Listed diagnoses include atypical anorexia nervosa, subthreshold bulimia nervosa, subthreshold BED, purging disorder, and night eating syndrome. Although the *DSM-5* Web site currently (March 2012) does not provide a definition of UFED, presumably, it is for cases in which clinicians conclude that a feeding or eating disorder is present but choose not to be more specific. Listing such conditions by name potentially provides industry with a "backdoor" way of promoting drugs for new indications by bestowing a more quasi-official status than NOS categories.

Cookbook Diagnosis

It has been argued that successive *DSM* editions have contributed to the "dumbing down" (Boyce, 2006) of psychiatric nosology and clinical and research practice into "mindless psychiatry" (Eisenberg, 1986; Lipowski, 1989). Diagnostic criteria generally do not explain causes of symptoms. In clinical practice, symptom cluster diagnoses can be like diagnosing "Cough Disorder" without elucidating the causes of cough (Parry, 2009).

Crucially, the *DSM-IV* introduction cautioned specifically against diagnoses being applied in a simplistic "cookbook" fashion, without careful consideration of clinical significance. However, this warning is often ignored. A major reason for "cookbook diagnosis" is external pressure. Harris (2011) quoted a psychiatrist who reported feeling compelled to diagnose in the first consultation:

> *years ago, he often saw patients 10 or more times before arriving at a diagnosis. Now, he makes that decision in the first 45-minute visit. "You have to have a diagnosis to get paid," he said with a shrug. "I play the game."*

Nonpsychiatrists are more likely to uncritically diagnose by the book, owing to limited training and experience. Armstrong and Earnshaw (2004) noted: "In diagnosing psychological disturbance GPs [PCPs] ignore major symptom areas that psychiatrists judge important." It is therefore very problematic that the *DSM-5* field trials totally exclude PCPs.

Example of PBD and Disruptive Mood Dysregulation Disorder

Frances (2010) has called PBD a "fad" diagnosis "epidemic" in the United States. He notes that PBD was constructed outside the strict *DSM-IV* criteria for bipolar disorder. However, the decontextualized descriptive psychiatric paradigm upon which *DSM-III* and *DSM-IV* are based allowed for PBD within the bipolar disorder NOS category. Diagnostic-upcoding pressures in the United States then fuelled the epidemic (Parry and Levin, 2012).

Despite a large research literature, PBD remains a contentious diagnosis. The traditional perspective that bipolar disorder rarely or almost never manifests before puberty still has wide support (Duffy, 2007; Kaplan, 2011; National Institute for Health and Clinical Excellence, 2006; Parry et al., 2009). A literature review shows that contextual factors such as attachment and maltreatment/developmental trauma are rarely considered in PBD research (Parry, 2012).

The *DSM-5* Childhood and Adolescent Disorders Work Group has proposed a new diagnostic entity: disruptive mood dysregulation disorder (DMDD) (APA, 2012). This cluster of irritable mood and aggressive behavior symptoms was previously called severe mood dysregulation, then temper dysregulation disorder with dysphoria (TDDD). The Work Group's justification for the new diagnosis is to counter the overdiagnosis of bipolar disorder in children (APA, 2010b). However, this may simply substitute one decontextualized problematic abbreviated acronym for childhood problems with another. The research underpinning DMDD also fails to consider contextual factors (Parry, 2012).

In his critique of PBD, Frances (2010) argues that TDDD is "too risky to be included in DSM-5 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." In a critical commentary on treatment guidelines for PBD in the *Journal of the American Academy of Child and Adolescent Psychiatry*, McClellan (2005) lamented: "the rate of psychotropic agents prescribed for preschoolers is skyrocketing… Labeling tantrums as a major mental illness lacks face validity and undermines credibility in our profession." However, labeling tantrums as mental illness is precisely what DMDD may do, although the criticism from McClellan, Frances, and others may be one reason why the *DSM-5* Work Group has dropped the word *temper* from the name.

CONCLUSION

New *DSM* diagnoses will provide opportunities to patent new or existing drugs for new indications. These drugs will be aggressively marketed, as will the new diagnoses. Diagnosis of subthreshold cases, via more lax criteria, will also be encouraged by pharmaceutical companies, particularly by harnessing the influence of KOLs.

Much of this will occur in primary care (where most mental health diagnosis and treatment occur) partly because of primary care clinicians' limited training and experience and also because mental disorders are less well defined in primary care. Combined with drug companies' marketing strategies to influence PCP prescribing, the lack of field-testing in primary care is particularly problematic. Rather than dismissing widespread criticism and placing the onus of proof on those who claim that inappropriate diagnosis and prescribing will escalate, the Task Force could have used its substantial resources to run representative trials in primary care to provide evidence of the likely impact of *DSM-5*.

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. This will also be to the detriment of the health system because of inappropriate resource allocation and opportunity costs.

DISCLOSURE

Melissa Raven is a member of Healthy Skepticism. Peter Parry is a member of Healthy Skepticism and has received payments from ACA, MHPN for online presentation and a lecture.

The authors declare no conflict of interest.

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Viewpoint

ANZJP

Australian & New Zealand Journal of Psychiatry
47(12) 1116–1118
DOI: 10.1177/0004867413509694

The autism spectrum disorder 'epidemic': Need for biopsychosocial formulation

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Introduction

In DSM-IV autism spectrum disorder (ASD) was defined as a cluster of lifelong neurodevelopmental disorders consisting of autistic disorder, Asperger's syndrome and pervasive developmental disorder not otherwise specified (PDD-NOS). ASDs can be disabling disorders and warrant multi-faceted assessments and interventions that are often required in some form across the lifespan.

The prevalence of ASDs has climbed dramatically in recent years and an over-diagnosis 'epidemic' has been suggested (Frances and Batstra, 2013). Partly to reduce over-diagnosis, ASDs have been consolidated in DSM-5, such that the subtypes are no longer used but all are referred to as ASD and severity is specified. ASD in DSM-5 is characterised by deficits in social communication and social interaction plus restricted repetitive behaviours, interests and activities (RRBs). Subjects without RRBs can be given a new DSM-5 diagnosis: social communication disorder. However, the DSM-5 field trials suggest most individuals currently diagnosed with ASDs will still have ASD under the new criteria. This allayed the fears of some advocacy groups.

We argue that there is an over-diagnosis 'epidemic' of ASDs, particularly in the paediatric population, and doubt that DSM-5 criteria will minimize this. The underlying drivers of this and similar over-diagnostic 'epidemics' is a combination of the descriptive symptom-focused and context-deficient nosology inherent in the DSM model combined with needs for services and other psychosocial gains associated with the use of diagnostic labels. A false ASD diagnosis can provide practical benefits such as financial and educational assistance, but it comes with side effects that may take years to be fully apparent.

Rising prevalence of ASDs

The prevalence of ASDs 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 (Fombonne, 2009). Studies published in the early 2000s reported prevalence ranging from 30 to 60 in 10,000, rising in recent years to 50 to 114 in 10,000 children (Baird et al., 2006). Prevalence rates for different subtypes of ASD have varied considerably. In most studies, the number of children with Asperger's syndrome, Rett's syndrome, and particularly PDD-NOS, has outnumbered children with autistic disorder by almost 2 to 1 (Rosenberg et al., 2009).

Postulated driving factors for the ASD 'epidemic'

Possible factors include changing diagnostic criteria, differing study methodologies, the coexistence of the disorder with a range of other conditions; heightened awareness of both professionals and the general public; an increase in services to meet the growing numbers of identified children which may further facilitate increased diagnosis; the ongoing investigation of possible aetiological factors; media publicity; and a professional and societal shift towards a biomedical perspective for human emotional and behavioural problems (Rutter, 2009). All of these can result in increased case identification, diagnostic substitution and diagnostic accretion.

To what extent the increase in ASD diagnoses is 'real' is a matter of debate. Reviews (Fombonne, 2009) suggest methodological differences between studies, referral patterns, diagnostic substitution, changes in the availability of services, the possible effects of migration into the area, and changes in public and professional awareness, make meaningful interpretation of prevalence rates and time trends across studies problematic.

There is evidence that a prime driver of diagnostic 'upcoding' is the coupling of ASD diagnoses to extra resource allocation from education and welfare services. In Queensland, specialist medical clinicians reported that, in the face of diagnostic uncertainty, they would provide an ASD diagnosis on a service provider's form even when diagnostic criteria had not been met (Skellern et al., 2005). This practice occurred more frequently in regard to meeting Queensland's

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access requirements for special education services. The authors caution, therefore, that numbers as high as 1 in 50 students should not be considered a true reflection of the ASD prevalence rate (Skellern et al., 2005).

Diagnostic upcoding has been implicated particularly amongst those with intellectual and learning disabilities, both in Australia (Skellern et al., 2005) and in Canada (Thivierge, 2008). However, it can occur amongst individuals of average or above average IQ as well.

Diagnostic instability

A systematic review of the diagnostic stability of ASD diagnoses found that whilst autistic disorder was relatively stable, Asperger's disorder and PDD-NOS were highly unstable. There was large variation in outcome studies but some showed up to 53% of children with Asperger's disorder and PDD-NOS later moved off the ASD spectrum (Woolfenden et al., 2012). It is unclear as yet whether collapsing the subcategories to a single ASD label as per DSM-5 will or won't assist diagnostic stability.

Need for diagnostic clarity

As in most conditions in child psychiatry the clinical presentation of individuals with ASD is marked by complex comorbid conditions and challenging psychosocial issues. There are several conditions that can mimic the symptoms of ASD especially in the absence of true restricted and repetitive behaviour (RRB), which is one of the key features for an ASD diagnosis; this has been emphasized strongly in DSM-5. A major challenge in the future would perhaps be how to differentiate technological addictions from the RRB of ASD. As many individuals with other neurodevelopmental conditions like speech and language disorders with social phobia can indulge in excessive gaming and internet use, which in turn can worsen their social and communication skills and mimic the symptoms of ASD. This is a diagnostic and therapeutic challenge with the potential to become an even greater issue when it is likely that some conditions would be funded under the National Disability Insurance Scheme and other conditions that are equally distressing for the sufferers won't.

Another issue in cases presenting with ASD features is the role of developmental trauma and insecure attachment (Alverez, 2004). This issue has been emotive and controversial given historical psychoanalytic theories that postulated a 'refrigerator mother' parenting style as a cause for autism. The paradigm shift to a more neurobiological perspective of ASD has been helpful but in light of the current ASD epidemic it seems the pendulum has swung too far. On the one hand there has been progress and benefits from a more neurobiological perspective in ASD which include reduction of parental guilt, focused evidence-based treatment, better understanding of the condition, better ways of dealing with the behaviour, etc. However, the potential disadvantages of a misdiagnosis or a narrow perspective in true cases are significant. An erroneous or too narrowly understood ASD diagnosis can have a self-fulfilling deleterious effect on a child's psychosocial development via self, family, teacher, peer and others' reduced expectations – the 'Pygmalion effect' (Batstra and Frances, 2012). The denial or ignoring of trauma, maltreatment and insecure attachment is widespread in society and even in the child psychiatric literature when that literature has a narrow DSM symptom focus (Parry and Levin, 2012).

Costs of over-diagnosis

Over-diagnosis creates the personal costs of: (i) stigma; (ii) reduced self and family expectations; and (iii) having to undergo unnecessary treatment and educational interventions. Symptoms of otherwise treatable psychiatric conditions can be conceptualized as a hallmark of ASD, potentially giving rise to therapeutic nihilism. The diagnosis can become a rationale to explain social withdrawal and justify continuing repetitive playing of online games. Social withdrawal can be further entrenched in the high functioning individuals who receive benefits from social services. The long-term future in such a situation might be an individual with a doubtful diagnosis of ASD, on a disability pension, socially isolated, spending hours on a computer immersed in virtual reality. This scenario must be borne in mind before diagnosing a high-functioning individual with ASD if there is any doubt.

The societal costs of over-diagnosis are the diversion of scarce educational, therapeutic and welfare resources away from those who most need them; and parental anxiety and confusion occasioned by the false 'epidemic'. Whilst funding announcements geared to ASD continue, society tends to respond eventually to false diagnostic epidemics. The Victorian public education system now mandates a multidisciplinary assessment including speech assessment. ASD funding is no longer provided in the absence of severe speech impairment. In such a situation children with genuine Asperger's disorder are likely to miss out.

Concluding remarks

Epidemiology, anecdotal reports and educational and service provider statistics reveal a growing 'epidemic' of ASDs. Changes to DSM-5 have partly been drafted to address over-diagnosis. However, the neo-Kraepelinian paradigm that underpins the DSM since DSM-III is part of the problem. Whilst symptom complexes can be more reliably described, individual developmental narrative and relative contribution of biopsychosocial contextual factors have generally been lost.

The checklist approach of the DSM has faced a barrage of criticism in recent years including an online

petition from the American Psychological Association, British Psychological Society and 50 other professional organisations (American Psychological Association, 2012). In particular it can be argued that the DSM model neglects attachment theory, maltreatment effects and developmental psychology and is more problematic in child and adolescent psychiatry (Dignam et al., 2010).

We argue that the bestowing of a DSM label of ASD, however useful and at times justified, is not a risk-free intervention. Rather, the gold standard of assessment and therapy in such cases is a thorough and often lengthy process of engagement with the child, family and school, leading to a comprehensive biopsychosocial formulation that considers all developmental and contextual factors in a child's life.

A tsunami of ASD diagnosed children and adolescents are entering adulthood. This will pose challenges for adult mental health services. Many young adults, maturing and moving out from their families, may find themselves being undiagnosed. 'Undiagnosed' may be welcomed by some but can be traumatic to an individual's self-concept. This delicate issue warrants a careful consideration (Patfield, 2011).

Keywords

Child psychiatry, autistic spectrum disorders, epidemic, diagnostic formulation

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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J. Clin. Med. **2014**, *3*, 334-347; doi:10.3390/jcm3020334

OPEN ACCESS
Journal of
Clinical Medicine
ISSN 2077-0383
www.mdpi.com/journal/jcm

Opinion

Biologism in Psychiatry: A Young Man's Experience of Being Diagnosed with "Pediatric Bipolar Disorder"

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Received: 9 December 2013; in revised form: 1 March 2014 / Accepted: 5 March 2014 / Published: 28 March 2014

Abstract: Pediatric bipolar disorder is a diagnosis that arose in the mid 1990s in the USA and has mostly remained confined to that nation. In this article a young American man (under a pseudonym) describes his experience of having the diagnosis throughout his adolescent years. His story was conveyed via correspondence and a meeting with the author, an Australian child psychiatrist. The young American's story reveals several issues that afflict contemporary psychiatry, particularly in the USA, where social and economic factors have contributed to the rise of a dominant biomedical paradigm—or "biologism". This focus on the "bio" to the relative exclusion of the "psychosocial" in both diagnosis and treatment can have serious consequences as this young man's story attests. The author explores aspects of his tale to analyze how the pediatric bipolar disorder "epidemic" arose and became emblematic of a dominant biologism. This narrative points to the need, depending on the service and country, to return to or retain/improve a balanced biopsychosocial perspective in child and adolescent mental health. Child psychiatry needs to advocate for health systems that support deeper listening to our patients. Then we can explore with them the full range of contextual factors that contribute to symptoms of individual and family distress.

Keywords: bipolar disorder; childhood; adolescence; psychiatric diagnosis; bioethics; pediatrics; medical sociology; iatrogenic disease; consumer participation; polypharmacy

1. Introduction

This article arises from a dialogue between myself, an Australian child and adolescent psychiatrist, and a young American man about his experience of psychiatric treatment over the course of his adolescent years. But in a way it starts much earlier with an article I read during psychiatry training in 1990. The article in the *Australian and New Zealand Journal of Psychiatry* by Australian professor Derek Silove left a distinct impression on me [1]. Silove reported:

> "A recent study visit to North America impressed on me the seriousness with which Australian psychiatry should consider the recent ideological shift in the USA to an extreme biological model of mental disorders. … In its most doctrinaire form, this monotheistic biologism rejects (or worse still, pays condescending lip service to) the roles of social, cultural and psychological factors in the genesis and treatment of psychiatric disorders and relegates mentalistic notions to the epiphenomenal waste heap."

Sixteen years later I was reminded of Silove's article when child psychiatric colleagues in Australia became aware of a controversial new diagnosis, "Pediatric Bipolar Disorder" (PBD), emanating from the USA. The death of a 4-year old girl in Boston on 3 psychotropics for PBD further highlighted the controversy. Colleagues and I critiqued a guest editorial favourable to PBD [2] that was published in the *Australian and New Zealand Journal of Psychiatry* [3], published an article on PBD "a controversy from America" [4] and conducted a survey of Australian and New Zealand child & adolescent psychiatrists on this issue [5].

My interest in PBD has led me to meet many excellent U.S. child psychiatry colleagues. Most hold views similar to the systemic biopsychosocial perspective I acquired in my training and practice of the profession here in Australia. They too express deep concern about the PBD "epidemic" in their nation. This article is not aimed at disparaging U.S. psychiatry. Nor is it to discount the true cases of bipolar disorder in young people that we see. However, I, like my American friends and other international colleagues, am motivated by a desire to see our field retain a balanced perspective. The PBD diagnostic epidemic is emblematic of the pressures and problems besetting the field. The DSM-5 [6] introduced a new diagnosis, Disruptive Mood Dysregulation Disorder (DMDD) specifically to curb the overdiagnosis of bipolar disorder in children and adolescents in the USA.

Because the USA leads many global trends, the PBD epidemic offers valuable lessons to global psychiatry and mental health care. Diagnostic upcoding factors—financial, social and bureaucratic pressures that foster increased use of particular diagnoses—are an international phenomenon. PBD and DMDD have their corollary in Australia, where an epidemic of Autistic Spectrum Disorder (ASD) relates to diagnostic upcoding factors embedded in educational and welfare benefits for children and families and health insurance rebates to health providers who diagnose ASD [7]. PBD did not receive sustained academic support in Australia or New Zealand and thus overdiagnosis of ASD seems to have played a similar role, though with much less accompanying medication.

Dialogue with a Young American Man Recovering from a Diagnosis of PBD

In 2008, I posted some thoughts on a mental health website forum discussion of PBD. A 20 years old young American man wrote eloquently on the forum of his personal experience. We corresponded by email and in a 2013 study trip of my own to the USA I met with him and heard his story face to face.

The young man, whom I shall call "Adam" (not his real name), is now in his mid 20th. His verbal recollections were virtually word for word what he'd reported in the emails 5 years earlier. He is doing well in his university studies, is widely read and very knowledgeable about psychiatry and health related politics. He has had no psychiatric diagnosis, nor any psychotropic medication, since leaving home in 2008. However he still struggles with the iatrogenic trauma of the diagnosis in his life. He recalled "about 30 hospital admissions" during the period of the PBD diagnosis. He was continuing to benefit from psychotherapy and apart from a sense of profound regret for a lost adolescence, he'd had no symptoms that would meet criteria for an "Axis I" psychiatric disorder in the past 5 years.

Adam's narrative is his subjective experience, and thus reliant on memory. However, he did show me several discharge summaries of his hospital admissions that corroborated his story. The documents included concern that Adam was suffering a degenerative neurological disorder at a time he was on multiple psychotropic medications but apparently without consideration of the cognitive impairing effects of the pharmacotherapy.

I shall now let "Adam" speak for himself, having only edited his emailed story for de-identification and to reduce repetition. The discussion will focus on the issues this articulate young man's account raises.

2. Adam's Story (From 2008/9 Email Exchange)

I don't mind sharing most anything about how my extensive psychiatric contact has affected me. I'm almost 21 now. I was 12 when first diagnosed. I had suffered depression and anxiety including severe OCD, which has since disappeared. It should also be mentioned 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. But unfortunately, he holds a faculty appointment at (edited—A PBD oriented child and adolescent psychiatry clinic).

Within about three months, I was on 8 different medications at one time. Very scientific treatment—all the best—several anticonvulsants, several antipsychotics, a couple of antidepressants and lithium too.

Things got so bad, that I ended up being referred to the neurology department, for different opinions about strange symptoms I began having on this cocktail. Which resulted in their giving me a working diagnosis of some kind of mitochondrial myopathy. "Bipolar plus mitochondrial disease" as it went. Which I have been told only recently could have been precipitated by the huge amounts of divalproex I was taking. The symptoms quickly disappeared when I coincidentally stopped the drug for unrelated reasons. Oh well, but it is a clear illustration of what one of the "best" academic medical centers in the world has to offer a struggling young boy.

Despite the sedation I survived high school and graduated near the top of my class.

I guess the biggest deficit this has left me with is sort of skewing the trajectory of my life. My mother fed into my "being sick" and gained a lot of collateral from it. But worse still, it caused complete neglect of any other possible causes of my problems. My parents in many ways tended to over-interpret every solitary behavior as part of the "disease". Everything in my life was screened through the filter of this immaterial "disease". I had enough stacked against me when I was so overwhelmed that they brought me to the psychiatrist in the first place. The neglect of my underlying depression and its being made worse by all the sedating drugs just caused me to just sort of collapse in on myself. And despite being well-liked, I had a difficult time establishing friendships in high school and elsewhere. I had to quit my swim team (when I was 12), something I was amazingly successful at and would have gone far with.

Meanwhile, none of this had the potential to correct itself because of my parents' own problems. So I have suffered for a long time and have been ostracized from my family.

I just think my case is so typical, because of the path things took, and the fact that I was diagnosed and treated by someone who is rubbing elbows everyday with world leading "experts" on this thing. Clearly, when a disturbed child walks into your office, divalproex, risperidone, and some basic parental psychoeducation, is not going to mean recovery for that child. But yet that's what their guidelines for "treatment" essentially are.

And to think, there's a trauma clinic right down the street—where I've gotten some treatment—and a stone's throw away, they're condemning kids to a diminished life. I'm personally of the belief that the children they're treating are NOT exceptional in any way, and have problems that could easily be ascribed to factors these people have no interest in considering in a serious manner. If everyone at their clinic presented with classical mania, (edit—the researchers) wouldn't be famous for anything. So they definitely do not have a clinic full of those kids.

2.1. In Response to a Further Question about Effect of the Diagnosis on His Sense of Self and Any Other Side-Effects

I never really believed the label myself like on an intellectual level, because like most young people, I always felt there was a reason for my behavior. I started to put some odd pieces of the puzzle together, like: I have this "disease" and it only manifests itself at home in the presence of 2–3 people that happen to be a part of my life. Then I began to wonder why I had never had another "manic" episode after a few years and realized that adults with the disorder don't always go years on end without a relapse of that kind of "episode".

I did however sort of believe it, only because if you tell a kid something long enough, they'll start to believe it. And of course, if I question my craziness, that's part of the "illness". So I got put in a double bind that really did make me feel like I was trapped or going crazy. 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.

But the worst part of this, which I have only been recently able to shake within the last year (2008/9), is the defectiveness I felt. Just kind of in some core way. Like I'm totally different. When I was younger, that feeling was a lot stronger and more prominent. Now I feel like a fool for

even having given thought after eight years to the question of whether I might go to sleep one night and wake up manic. I decided with my (new) psychiatrist's support a year ago to stop my medicines. I'm not doing especially well now, but I have at least been able to shake the feelings the diagnosis itself carved into me. The same can't be said for its physical and social effects though.

I am also gay. And this focus on an immaterial disease brought the issue into my own mind prematurely because of all this psychiatric treatment and it ensured that my family and doctors would completely neglect it (the focus was the "disease"). It made something that isn't normally a cakewalk something extraordinarily difficult and complicated.

As far as ownership of my behaviors and emotions go, I never believed the diagnosis on an intellectual level and I always knew there were reasons for my behavior, I just couldn't really recognize them or name them. So I think a question like that would, sadly, be better asked of my parents. How did it affect their perception of everything? It didn't make me feel not responsible for my actions and on some level I was at least partly sure I wasn't some defective, degenerating, out-of-control machine.

The mitochondrial disorder thing was a disaster. The testing and consultation dragged out for months. At one point my mom told me they didn't know if my brain would keep "degenerating". In effect, "you're gonna die". And my psychiatrist was really out to lunch on that one, again. So that experience just profoundly deepened my ignored depression.

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.

One very embarrassing problem, which I imagine divalproex is involved with and which my psychiatrist certainly never imagined asking about, was my pubic hair began to fall out. Yep. The amount and frequency that came out was not normal. It was not good.

I also had severe weight gain. From my first contact with these psychotropics, after only 4 months I gained over 50 lbs. I would subsequently lose it when I would stop the medication myself and then gain it back when I was forced back on the medications. This cycle repeated itself 5 times over 8 years. Obviously I couldn't go back to swimming. Having almost qualified for national swimming championships a year before my diagnosis, I didn't recognize myself as the cow I was forced to become. This was very troubling. I lost control of my body. After one cycle I gained about 85 lbs in 6 months.

I had sexual dysfunction that would only abate when I stopped the drugs. Every SSRI drug I happened to be put on completely obliterated my sex drive. They were the worst.

I also wonder having never had my prolactin levels tested and having been on risperidone and divalproex for about 7 growing years whether I should get my bone mineral density tested.

I am in psychotherapy, and with a good psychotherapist (finally!). It's helping a lot.

Sorry for being so long-winded, but that's the basic extent of things. And I don't mind you sharing any of it. I read your papers and letters published in the journals, and I have to tell you it gave me a lot of hope and sort of made me feel like the world is a little less crazy.

2.2. Further Information

In the face-to-face meeting in 2013, Adam said that his siblings, now all adults, had worked through their issues (partly with therapy) and were reconciled on very good terms. They now had shared insight into the intergenerational patterns of disrupted attachment involving their grandparents and parents. The precipitant to their mother's investment in Adam's PBD diagnosis appeared to be a bereavement crisis following the deaths of the maternal grandparents. Adam said he and his siblings were concerned about their mother, who, after Adam left the home, developed a preoccupation with a range of medical complaints and sought out different medical specialists despite normal tests for her alleged medical disorders.

Adam also recalled that early in his treatment he received an SSRI that caused him to have akathisia and agitation with insomnia causing intense frustration—but no core symptoms of mania such as euphoria, flight of ideas or grandiosity. This was diagnosed as "mania". Afterwards, he never had the reaction to the same extent with further SSRIs. From my inquiries in our 2013 discussion he described how he had never had any core manic symptoms at any point.

If some readers remain skeptical of Adam's story and his current wellbeing then a mental state examination is worth adding. Across a dinner table over a couple of hours, both I and my psychiatrist colleague (Dr. Anja Kriegeskotten) found ourselves communicating with a very genuine, perfectly sane and intelligent young man with absolutely normal emotional reactivity and good sense of humor. He showed deep insight into the social dynamics of his family and the health system that had engulfed his adolescence. A warm and candid rapport was easily established.

3. Discussion

3.1. Decontextualized Psychiatry

Adam said: "there was a lot the psychiatrist should have asked about". Psychiatric symptoms do not occur in a vacuum. In Adam's words—"there is always context".

The political history of psychiatry that led to DSM-III in 1980 explains why psychiatric nosology became decontextualized. Broadly speaking psychiatric nosology has been a struggle between two different perspectives, embodied in (1) Emil Kraepelin's more "medical model" of categorization by symptoms and course of illness, and (2) 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. DSM-III adopted a nomothetic, "neo-Kraepelinian" model of diagnosis, based on symptom criteria checklists. This arose out of the need for reliability in diagnosis following an era dominated by psychoanalysis and subjectively inferred psychodynamic conflicts. There was also great geographical variation in the diagnosis of schizophrenia between the USA and Europe that called for more strictly defined diagnostic methodology. But lost was the "Meyerian" ideographic model for diagnosis (partly embodied in DSM-I and DSM-II) that viewed psychiatric syndromes as arising out of individual lives with multiple interactive biopsychosocial causations [8].

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" [9]. Adam is not alone to suffer from misdiagnosis or diagnosis without consideration of context. The recent publication of DSM-5 occurred amidst controversy. Thousands of mental health clinicians and over 50 mental health organizations signed an online open letter protesting the decontextualized nature of the DSM, the open letter stated:

> "… (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." [10].

Robert Spitzer, head of the APA's DSM-III committee, that emphasized the nomothetic over the ideographic in psychiatric nosology, recently revised his viewpoint in a foreword to the book *The Loss of Sadness: How Psychiatry Transformed Normal Sorrow into Major Depressive Disorder* [11]:

> "(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."

Adam and his family had a lot of relational suffering. It may have been 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 insight into these dynamics. That insight has been liberating for them.

3.2. Pediatric Bipolar Disorder—Emblematic Diagnosis for Decontextualization

The head of the DSM-IV committee, Allen Frances, has criticized aspects of DSM-5. He also criticized PBD [12]. Although Frances noted that strict adherence to DSM-IV criteria would've ruled out PBD, the nomothetic and by default biomedical model of DSM-IV allowed PBD to flourish within the Bipolar Disorder—Not Otherwise Specified (BD-NOS) category. A recent article [13] goes further to criticize 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."

Several factors appear to have fueled the PBD epidemic: The pharmaceutical industry's influence on research, medical education and consumer groups; a desire for a blame-free biological explanation to distressing family problems; a human individual and societal need to repress trauma; and diagnostic upcoding in the U.S. health system that rations treatment according to DSM diagnoses [14]. To this could be added academic hubris: Adam noted that by defining a "new" disorder, the academic child psychiatric center that he attended gained a degree of fame.

The PBD academic literature is grossly lacking in research into contextual factors. A systematic review [15] of over a thousand PBD articles for terms such as attachment theory, maltreatment and child neglect found these terms to be almost completely absent. PTSD, trauma and child abuse terms were infrequently referred to and generally only in passing. Rates of physical abuse and sexual abuse in cohorts of research subjects from the two academic child psychiatric centers that pioneered PBD

were far below rates in community surveys and emotional abuse appears to have not been considered at all. The methodology in PBD research leans heavily on structured parent interviews. As in research, so in clinical practice. As Adam informed me, the sessions with his psychiatrist involved his mother and the psychiatrist discussing his symptoms and little space for he to ever talk about the physical and emotional abuse by his brother, or the background to the conflict with his mother.

DSM-5 has introduced DMDD with the primary rationale to curb the diagnosis of PBD. However DMDD still embodies the same decontextualized model. A similar systematic literature review of 76 articles found minimal mention of attachment, maltreatment and parenting and family dynamic factors [16]. It seems possible that without recognition of context, a child could go through a similar experience to Adam with a DMDD label. In contrast, another diagnosis submitted for inclusion in DSM-5, Developmental Trauma Disorder (DTD) [17], embedded contextual factors in its criteria. The DSM-5 committee rejected DTD mainly on the basis that symptoms overlapped with other disorders, even though the same critique has been leveled at DMDD [18]. It appears that many researchers prefer to count symptoms rather than explore where they come from.

3.3. Over-Medicating and Side-Effects

Adam described a staggering amount of psychotropic polypharmacy with a litany of side-effects. The treatment Adam received could trigger Medical Board investigation in Australia, yet Adam informed me his legal inquiries indicated his treatment would be deemed "standard practice" where he lived. Nonetheless there is increasing criticism of these medication practices with reports of iatrogenic morbidity and mortality in the U.S. media [19] and academic literature [20]. A health system that forces many child psychiatrists into brief "med checks" is seen as a serious problem. An op-ed in the *Los Angeles Times* by A/Prof Laurel Williams expounds on these problems [21].

Adam had an akathisia/agitation reaction to an SSRI at age 12. These are now well described in the literature [22,23]. However in the 1990s there was dispute about such reactions, and pharmaceutical manufacturers tended to deny the existence of SSRI induced agitation. I recall seeing several adolescents develop the reaction when I worked on a mood disorders unit for young people in the mid-1990s. At the time I prescribed SSRIs liberally. We now know that at least some published SSRI drug trials suppressed data about these reactions [24]. Patients like Adam suffered if their treating psychiatrists were kept in the dark about side-effects by the academic literature. For example, I recall prescribing quetiapine to help patients on antipsychotics lose weight—on the basis of fraudulent studies sponsored by AstraZeneca (London, UK), the manufacturer of quetiapine (Seroquel) [25].

3.4. The Iatrogenic Harm of Erroneous Labeling

Adam eloquently describes the impact of the diagnosis upon his sense of identity and familial relationships. The central task of adolescence is individuation [26]. Identity development can be severely damaged by a misdiagnosis of PBD, where one's every thought and feeling can be doubted as whether it is a part of self or, as Adam says, some "immaterial disease". As Adam also indicates, the impact of sedating medications on subjective experience adds to the impairment. Despite his success at university and the psychotherapy that has helped him work through his family conflicts, he still feels a disturbing lack of connection with his sedated adolescent years.

This damage to identity formation in children with PBD diagnoses has been noted [27,28]. Even where biomedical explanations may be warranted, there is evidence that a biomedical explanation is likely to foster greater rather than less stigma and induce "prognostic pessimism" [29]. Adam is at the crest of a tsunami of thousands who've grown up with the PBD diagnosis. Many of these young adults do not have the resources Adam has marshaled. It is an area that demands further research. With PBD and other diagnoses psychiatrists are often faced with having to "undiagnose" patients, and given the entanglement of label with identity the task of "undiagnosing" requires tact and much support [30].

3.5. Projective Identification and "Munchausen's by Proxy"

It is traditional wisdom in child psychiatry that parents often project unresolved issues onto their offspring. The children may identify and act out accordingly. Some 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 disavowed dependency needs. It appears that once Adam left the home his mother produced spurious medical symptoms and diagnoses for herself, in other words her own likely case of Munchausen's disorder.

An early critique of PBD [31] noted that not only could parents have a psychological investment in the PBD diagnosis, but so too could 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".

This is not to say that there need be any negligence or mal-intent at all. Factors operate at systemic and subconscious levels. Adam's mother, his doctors and others no doubt acted with Adam's best interests in mind. A dominant paradigm is hard to see when you're living and working within it.

3.6. A Paradigm Problem in Psychiatry

Silove [1] (1990) in his prophetic article on psychiatric trends in North America, referenced both the eminent U.S. child psychiatrist Eisenberg [32] and a president of the Canadian Psychiatric Association, Lipowski [33], both of whom used the terms "brainless psychiatry" and "mindless psychiatry". The mid 20th century hegemony of Freudian psychoanalysis tended at its extreme to be a "brainless" model that Eisenberg and Lipowski were highly critical of. But the thrust of their late 1980s warnings concerned the rise of "mindless" psychiatry, or, as Silove called it, "biologism".

What is it but "biologism" that influenced Adam's psychiatrist and other doctors to misconstrue parent-child conflict as mania, prescribe him so much medication and misdiagnose polypharmacy side-effects as a neurological disorder involving months of high-tech investigations?

In addition to being a method of inquiry, science is a social process and there is a vast research literature concerning the sociology of science. Scientific disciplines do not build on knowledge in a purely linear fashion, but at times undergo dramatic upheavals according to paradigm shifts [34]. The dominant paradigm governs what is acceptable to study, research, publish and practice. Softer sciences like psychiatry can be more susceptible to extreme paradigm shifts. The history of psychiatry reflects this. The issue is not simply an academic one (pun intended). What is emphasized in teaching and research plays out in practice—with real life consequences, as Adam well describes.

3.7. Training in Psychiatry

Silove [1] described a narrowing of psychiatric training by 1990 in the USA:

> "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."

Silove was hopeful Australasian psychiatry's grounding in the "eclectic" 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. The presentation of a diagnostic case formulation in these exams—a narrative of the patient's psychopathology within the developmental biopsychosocial context—is still more valued by the RANZCP examiners, as I know from my time as a case histories examiner, than symptom criteria-based diagnoses such as in DSM-5 or ICD-10.

Nonetheless biologism in psychiatry is a global issue. Boyce [35], in a presidential address to the RANZCP annual congress titled "Restoring Wisdom to the Practice of Psychiatry", noted in Australia and New Zealand there had also been a:

> "… dumbing down" of psychiatry (due to) "increased service demand, the deification of DSM, the influence of the pharmaceutical industry, a misunderstanding of evidence-based medicine, managerialism and the influence of consumerism."

However unlike Australasia where the focus is still generally on clinical need, the U.S. health insurance industry rations treatment according to DSM diagnoses and U.S. academic psychiatry and education has been more dependent on pharmaceutical funding than in Australasia.

On my recent study trip to the USA I was privileged to visit some centers of excellent holistic psychiatric training, but these may not reflect the norm. At the 2013 APA annual meeting in San Francisco, a psychiatric resident told me how his group had been practicing for their board exams. Their experienced tutor asked for the "diagnostic formulation" for the patient who was interviewed, but none of the residents had heard of a "formulation" in their entire psychiatric training. I was also informed that the U.S. National Board of Medical Specialties (NBMS) exams were going to be devoid of real life patients, using written clinical vignettes in future.

Of U.S. psychiatry training, Tasman [36] wrote:

> "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."

The loss of the biopsychosocial diagnostic formulation compounds the demise of psychodynamic theory in psychiatric training. In practice this means that the patient's inner life is devalued or ignored, surface symptoms are taken at face value and underlying causation and meanings may remain unexplored. This could explain why a highly qualified psychiatrist with strong academic credentials

and with the best intentions, could, as Adam describes, fail to explore his inner thoughts and feelings and the family context.

4. Conclusions

Psychiatry needs a paradigm shift to one that is neither "brainless" nor mindless". Bracken *et al.* [37] described the dominant paradigm in psychiatry as a "technological paradigm" that has relegated relationships, meanings and values to secondary concerns and focused on symptomatology and interventions "independent of context". 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."

It should be obvious actually.

Stepping out into the San Franciscan sunshine at the 2013 APA conference, I was greeted by several hundred protestors chanting in loud unison: "APA, APA, how many kids did you drug today?" The protestors were from the Scientology backed Citizens Commission for Human Rights (CCHR). Whilst I did not entertain joining them—I am a psychotropic prescriber after all—I couldn't help but ponder the question that echoed around the surrounding skyscrapers.

I heard that Prof. Joel Paris, editor-in-chief of the *Canadian Journal of Psychiatry* stated in a presentation at the 2012 APA annual meeting:

> "When psychiatrists 50 years from now look back on our current era in psychiatry, they will understand that the diagnosis of pediatric bipolar disorder is the greatest scandal to ever befall psychiatry." Prof. Paris confirmed: "This is exactly what I said."
>
> —Personal Communication [38]

What Adam went through was scandalous, even if well-meaning. But his story demands action now and shouldn't have to wait for the verdict of history. He is at the crest of a tsunami of young people who have been affected by the PBD diagnosis. Others are starting to voice their stories as in documentaries like "Letters from Generation Rx" [39]. Their stories need to be heard. Psychiatry needs to be grounded in listening to our patients. By listening to their full stories and by understanding the full context of whatever problems are brought forth, we may offer more tailored beneficial assistance across the biopsychosocial spectrum, and, at the very least, do no harm.

Acknowledgments

I am very grateful to "Adam" who has shown courage in sharing his story and allowing me to view documentary evidence of his treatment. I am also grateful to Anja Kriegeskotten for comments regarding the manuscript.

Conflicts of Interest

The author declares no conflict of interest.

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LETTERS TO THE EDITOR

Stark Discrepancy in Pediatric Bipolar Diagnoses Between the US and UK/Australia

To the Editor:

James *et al.*[1] reported stark differences in inpatient diagnostic rates of pediatric bipolar disorder (PBD) between the United Kingdom and the United States in the June 2014 issue of the *Journal*. The scale of the discrepancy is huge: by 5 years of age, the rate of PBD discharge diagnoses in US inpatient units exceeded the rate for BD diagnoses by 19 years of age in the United Kingdom!

Australia and New Zealand are closer to the British rates than to those of the United States.[2] In the childhood-early adolescent inpatient unit at the Royal Children's Hospital, Brisbane, Australia, there were 505 patients (3–15 years old, mean 9.8 years) admitted over 5 years, from July 1, 2009 to July 1, 2014. Only 2 had *International Classification of Diseases, Tenth Revision (ICD-10)* code F31 bipolar spectrum diagnoses: a 14-year-old boy with code F31.3 (bipolar disorder: mild-moderate depression) and a 14-year-old girl with code 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 code 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. Thus, prepubertal cases of BD in Australia's third largest state are almost nonexistent.

Stringaris and Youngstrom[3] explored the US-UK discrepancy in their editorial on the article by James *et al.* ("Unpacking the Differences in US/UK Rates of Clinical Diagnoses of Early-Onset Bipolar Disorder," June 2014), referencing a meta-analysis[4] positing the "true prevalence of [pediatric] BD does not vary between countries" and is 1.8%, so the problem must be in the "administrative prevalence" (p. 609). In fact, the meta-analysis they cited has significant methodologic problems and does not address prepubertal childhood rates.[5]

As Stringaris and Youngstrom speculated, differences in discharge rates more likely reflect differences in diagnosing PBD. US psychiatrists use a "wider construct of BD" than their British counterparts. Evidence for this includes US-UK divergence on clinical vignettes,[6] where the US *DSM* focus on checking operationalized criteria contrasts with the *ICD* focus on pattern recognition. Pattern recognition requires experience seeing patients longitudinally. US insurance companies tend to only cover short lengths of stay, necessitating brief assessments. Thus, US clinicians are deprived of vital experience in such longitudinal phenomenology. Note the huge differences in length of stay between the 2 countries.

In addition, researchers use and interpret standardized assessments differently based on a "liberal" (more the US view) or "conservative" (more the non-US view) orientation.[5] Thus, the use of existing research measurements will not clarify the differences or bring them more in line.

In addition to other explanations offered by Stringaris and Youngstrom, diagnostic up-coding for reimbursement purposes is not necessary in most health care systems outside US-managed care. Pharmaceutical company influence on parents through direct-to-consumer advertising and support of PBD parent advocacy groups has not occurred outside the United States. The significant financial support of PBD researchers by the pharmaceutical industry has been minimal outside the United States. The capacity to focus on a biopsychosocial case formulation and multimodal management of emotional and behavioral problems is a common feature of clinical practice in non-US health care, leading to less emphasis on an Axis I diagnosis.[7]

Stringaris and Youngstrom expressed the opinion that a minority of UK child psychiatrists doubt the existence of PBD. However, a debate on PBD at the 2010 Royal College of Psychiatrists' Faculty of Child and Adolescent Psychiatry conference indicated most UK child psychiatrists dispute the validity of US PBD phenotypes. This skepticism concurs with the 2006 British National Institute for Health and Clinical Excellence guidelines that PBD phenotypes were research hypotheses only and that there were 0 inpatient BD diagnoses in preadolescent British children from 2000 through 2010.

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Ethics approval for the release of anonymized patient data from the Child and Family Therapy Unit (psychiatric inpatient unit) at the Royal Children's Hospital, Herston, Brisbane, Queensland, Australia was obtained. The reference number for this ethics approval is HREC/14/QRCH/118. The contact person for data analysis is Ms. Rebekah Stewart (Rebekah.Stewart2@health.qld.gov.au).

Drs. Parry and Richards report no biomedical financial interests or potential conflicts of interest.

http://dx.doi.org/10.1016/j.jaac.2014.08.012

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Drs. Stringaris and Youngstrom reply:

We thank Drs. Parry and Richards for their response to our editorial related to the article by James *et al.* in the June 2014 issue of the *Journal*. The authors raise a number of important points that we would like to take up for further discussion.

First, the authors refer to "US pediatric bipolar (PBD) phenotypes" throughout the letter. We would caution against such generalizations. There are important differences in approaches to PBD within the United States. Indeed, most of the scientific debate about PBD happened between US groups.

Second, 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.

Third, the authors suggest that long hospital stays are better because they allow clinicians to take a "longitudinal" view of patients. This is a problematic argument. Children's hospital admissions should not be for the benefit of clinicians' observations; they should be planned strictly to serve young people and families. Good psychiatrists are perfectly capable of observing their patients in their natural milieu, namely the community.

Fourth, 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.

Fifth, the authors seem to suggest that an increase in the rates of PBD is a bad thing in its own right. This is hard to defend: depression was not formerly a diagnosis for young people, yet it thankfully is now, with characteristics similar to those of adult depression.[1] Similarly, the rates of recognition of epilepsy increased because people have been less inclined to ascribe it to metaphysical causes.

Sixth, the assertion that psychiatric diagnoses must be corroborated by multiple informants to be confirmed flies in the face of clinical reality. Reporter agreement in child psychiatry is reassuring but is typically modest across diagnoses.[2] Although overt mania will rarely go unnoticed by a young person's relatives, hypomania and impairing manic symptoms are devastatingly under-recognized, even in adults.[3]

As clearly stated in our letter, none of us takes the position that all candidate BD phenotypes in the United States (or elsewhere) correspond to true BD. In fact, we have devoted part of our scientific careers to testing (and often rejecting) such phenotypes.[4] We also noted in our editorial that there are some plausible reasons why such rates may have been inflated. Yet a rapidly growing body of solid empirical research clearly shows that BD does occur in youth, and that it does merit more attention than it has received so far. The authors say that where they themselves can afford to place "less emphasis on an Axis-I diagnosis." Maybe so, but the question is whether avoiding a diagnosis is good for patients. A good biopsychosocial formulation does not take away the need for careful diagnosis—we actually believe that it makes it imperative. BD is among the top 10 causes of the global burden of disease,[5] with an annual cost of £2 billion ($3.4 billion) in the United

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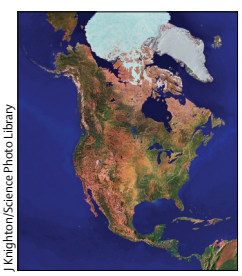
Reification of the paediatric bipolar hypothesis in the USA



Lancet Psychiatry 2014

Published Online December 1, 2014 http://dx.doi.org/10.1016/S2215-0366(14)00075-3

This online publication has been corrected. The corrected version first appeared at thelancet.com/psychiatry on January 8, 2014

Paediatric bipolar disorder was first proposed as a research hypothesis in two articles in 1995.[1,2] Two research groups postulated that mania might occur in early childhood when it manifests differently from adulthood—as multiple mood episodes per day (ultradian cycling)[1] or chronic irritability generally without elevated mood.[2] Paediatric bipolar disorder rapidly entered clinical practice in the USA via the Diagnostic and Statistical Manual of Mental Disorders (DSM) category of bipolar disorder–not otherwise specified. By 2004, bipolar diagnoses in children and adolescents had increased 40 times in US primary health care[3] and become the most common diagnosis in preadolescent inpatient units.[4] Between 2000 and 2010, mean bipolar diagnoses for children aged up to 19 years were 100·9 per 100 000 children in 50 US inpatient units, peaking at 140 per 100 000 children in 2006, then falling back to the mean by 2010.[5]

By contrast, the rate was 1·4 per 100 000 children and adolescents aged up to 19 years from all English inpatient units with no preadolescent cases. US cases at age 5 years exceeded English cases at age 19.[5] Preadolescent cases were very rare in other clinical cohorts in the UK, Germany, Denmark, and Finland,[5] in line with the opinion of child psychiatrists in Australasia.[6]

So why did the paediatric bipolar disorder diagnostic epidemic occur and remain mostly confined to the USA? Among more than a thousand, mostly American, articles about paediatric bipolar disorder,[7] a few US psychiatrists and paediatricians have been vocal critics. They noted that diagnostic criteria for paediatric bipolar disorder deviate from strict DSM criteria;[8–10] symptom-checklist approaches to diagnosis did not account for developmental and contextual factors;[9,11,12] trauma and attachment disruption were overlooked;[9,11] the pharmaceutical industry collaborated with key opinion leaders and researchers of paediatric bipolar disorder;[10] and that the US health system often mandates more serious diagnoses in order to provide reimbursement, which fosters diagnostic upcoding.[4,10,13] For example, a child psychiatrist in Texas described a boy aged 10 years diagnosed with paediatric bipolar disorder who was being given eight concurrent psychotropic drugs. The psychiatrist challenged the diagnosis and noted that direct marketing has led the US public to "believe there is a drug to solve every discomfort and every mood" and that US doctors are so constrained by the health system that it's "easier to medicate symptoms than to do a full assessment".[13]

In our view, the paediatric bipolar disorder diagnostic epidemic also reflected a broader problem of reification of diagnoses; that simply naming an occurrence confirms its existence as a concrete entity. DSM-III adopted a descriptive model that restricted the role of causes in nosology.[14] This restriction minimised the consideration of developmental, relational, and systemic factors. A systematic literature review of articles about paediatric bipolar disorder published from 1995 to 2010 noted almost no mention of the terms "attachment", "neglect", or "maltreatment", and very few mentions of the terms "trauma", "PTSD" (although PTSD is proposed as a possible sequelae to childhood mania), "physical abuse", or "sexual abuse", and few mentions of the terms "verbal abuse" or "emotional abuse" in paediatric bipolar disorder research cohorts.[7] In an era of dominant pharmaceutical industry-funding and marketing, the presumption of biomedical causes for DSM disorders filled the aetiological space.

Spielmans and Parry[15] have described the concept of marketing-based medicine (MBM) from their research into internal pharmaceutical-industry documents. MBM aims to expand markets for on-patent drugs. Diagnoses including bipolar disorder that warrant treatment with on-patent atypical antipsychotics received vigorous industry promotion via research funding, sponsored medical education, marketing to clinicians and—in the USA—direct marketing to

the public.[15] In particular, key opinion leaders who supported the concept of paediatric bipolar disorder received greater industry support than those who didn't.[16] Diagnoses of paediatric bipolar disorder helped to increase use of on-patent antipsychotic drugs in children.[17]

Although reification provides an air of validity, and MBM contributes to overdiagnosis, diagnostic upcoding provides additional treatment resources. DSM diagnoses such as attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, adjustment and anxiety disorders, and parent–child relational problems are often underfunded in US health and education systems.[4,13,18] Diagnoses of more serious conditions such as paediatric bipolar disorder often allow for greater reimbursement and access to resources than less serious ones.

European and Australasian health jurisdictions do not generally allocate funding by diagnosis, which is a possible reason why the paediatric bipolar disorder diagnosis has not gained traction in these areas. Such jurisdictions help to formulate biopsychosocial diagnoses that emphasise the interplay of developmental and contextual factors. However, autistic spectrum disorder accrues educational and welfare resources in Australia that led to a diagnostic epidemic of autistic spectrum disorder in this country.[19]

DSM-5 has introduced the diagnosis of disruptive mood dysregulation disorder to curb US rates of overdiagnosing paediatric bipolar disorder.[20,21] However, a systematic review of 76 articles about disruptive mood dysregulation disorder showed a similar absence of attachment, trauma, and maltreatment factors, as with paediatric bipolar disorder.[20] The risk with a diagnosis of disruptive mood dysregulation disorder is another reified label to justify over-reliance on polypharmacy interventions and neglect of psychosocial factors.

Lessons should therefore be learned from paediatric bipolar disorder by global child psychiatry, paediatrics, and health care systems. The US paediatric bipolar disorder diagnosis epidemic resulted from the constraints of a biomedical framework for research and clinical practice. Diagnoses such as paediatric bipolar disorder, attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, autistic spectrum disorder, or disruptive mood dysregulation disorder have their meanings, but individual children and their family or carers need child psychiatrists and paediatricians to apply the traditional biopsychosocial model, and to have the time and resources to do so.

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We declare no competing interests.

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Thanks to our peer-reviewers in 2014

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While still in its first year, *The Lancet Psychiatry* has already published a substantial number of articles and many more have been sent for review. While each paper clearly represents a huge amount of work by the authors, the published work also reflects the dedication and expertise of our peer reviewers, who so generously give up their time to ensure that each Article, Review, or Personal View reaches the highest standards and is of interest and relevance to our readers. The editorial team at *The Lancet Psychiatry* would like to take this opportunity to thank our peer reviewers and our Editorial Board who have contributed to our successful first issues. We are very grateful to all those authors who have sent us their papers. While it is too early to judge clinical impact or citations, many of the papers have proven very popular in terms of downloads, so our final thanks go to our readers. The names of the experts who reviewed papers for us in 2014 are published on our website (appendix); those who reviewed three papers or more are marked with an asterisk. We look forward to continuing our work in 2015, to make *The Lancet Psychiatry* a leading journal, with a clear focus on excellence in research and clinical care.

Niall Boyce, Joan Marsh, and Catherine Quarini
The Lancet Psychiatry, 125 London Wall, London, EC2Y 5AS

Corrections

Peter I Parry, Stephen Allison, Tarun Bastiampillai. Reification of the paediatric bipolar hypothesis in the USA. Lancet Psychiatry *2014; published online Dec 1. http://dx.doi.org/10.1016/S2215-0366(14)00075-3*—In this Comment, the following sentence is incorrect: DSM-III adopted a descriptive model of paediatric bipolar disorder that restricted the role of causes in nosology. The correct wording should be: DSM-III adopted a descriptive model of nosology that for most disorders in the manual restricted the role of causes. These changes have been made to the online version as of Jan 8, 2014. The print version is correct.

ANZJP

Australian & New Zealand Journal of Psychiatry
1–1

Letter

Paediatric bipolar disorder: What are the dangers of treating a hypothetical disorder as a real disease?

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DOI: 10.1177/0004867416670016

To the Editor

Amerio et al. (2016) have recently 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?

PBD began as an interesting research question, investigated by child psychiatrists working in US universities during the 1990s. They wondered whether adult bipolar disorder (BD) could be detected early in life and treatment instituted from childhood. Subsequent US studies focused on symptom profiles among young children including offspring of adults diagnosed with BD. However, after many studies over two decades, it was found to 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). By definition, it is challenging to predict relatively rare outcomes from variable collections of frequently occurring antecedents.

While PBD remained an interesting research hypothesis in Ivy League universities, it presented few dangers. However, the concept was prematurely translated into clinical practice, resulting in the widespread off-label prescribing of a broad range of adult psychotropic medications for children and adolescents, especially in the United States (Malhi, 2016). For instance, Amerio et al. (2016) located seven clinical studies of PBD–OCD, which included the use of clozapine (for a 13-year-old boy), lithium (including a 4-year-old boy), lamotragine, divalproex sodium, olanzapine, risperidone, quetiapine, aripiprazole, clonazepam, clomipramine and escitalopram among others (Table 1: p. 595). The risks and benefits of these 11 medications have not been fully investigated with randomised controlled trials in children, but the original clinical studies reported a variety of side effects such as increased appetite, sedation, slurred speech, gait disturbance, low blood pressure, neurological symptoms, agitation, manic switch and suicidal intent.

In Australia and New Zealand, child psychiatrists have been careful observers of the US PBD phenomenon with the vast majority choosing not to adopt the hypothesis into clinical practice (Parry et al., 2009). This caution was well founded, as it has proved impossible to diagnose PBD accurately, and adult medications present iatrogenic dangers for children.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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I was reminded of this campaign while attending the recent RANZCP International Congress. While introducing one of the keynote speakers, the introducer announced the first syllable of his first name, and then unsure how to pronounce the rest, went on to his last name. Then, the speaker after him also called him by his truncated first name.

Late I met the Speaker and asked him how he felt about being called by an incorrect first name. I told him why I was asking. When I had first gone to the United Kingdom in the late 1990s to do my postgraduate training, I had been told that my name was too difficult to pronounce so I will have to come up with a simpler first name. I had replied, 'If I can make an effort to pronounce your name correctly, I expect you to do the same'.

The Speaker and I traded some funny, and some not so funny, stories about our experiences with our names. He basically told me that he had accepted that that is the way it is going to be, and there was nothing he could do about it. The most heartbreaking story he told me was that one long-term colleague mistook a paper as being authored by him just because he had never known his full first name, to which he had replied, 'I know all of us look the same to you but please read the full name first next time'.

I have coined a new term for this phenomenon which is 'Nominal Colonialism'. It goes like this, 'You are now in MY country mate. Do not expect me to waste time on learning to pronounce your foreign-sounding, unfamiliar name. Change it to something simple that I can say easily'. I just wonder if colleagues realize how unfair it is to coerce other colleagues into simplifying their names, or to keep calling them with wrong, truncated or altered names.

Maybe the RANZCP can learn a thing or two about cultural diversity from Palmerston North Girls' High School.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Paediatric bipolar disorder: Reality or myth?

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DOI: 10.1177/0004867417746002

To the Editor

'Paediatric bipolar disorder' (PBD) is a frequently made diagnosis in the United States. The diagnosis is based on descriptions of pre-pubertal 'mania' with ultra rapid mood cycles and is often comorbid with neurodevelopmental disorders such as attention-deficit hyperactivity disorder (Duffy and Malhi, 2017). However, these frequently occurring forms of childhood mood lability are unlikely to be due to the early onset of bipolar disorder. As Duffy and Malhi (2017) noted in a recent Editorial, '*the early course of bipolar disorder charted from prospective studies of high-risk offspring is strikingly different from that derived from studies of clinical samples of children diagnosed with paediatric bipolar disorder*' (p. 761).

A recent re-analysis of epidemiological studies drew similar conclusions (Parry et al., 2017). Previously, it has been argued that PBD is common but underdiagnosed outside the United States. The average population prevalence has been estimated to be as high as 1.8% among 7–21 year olds. However, we re-analysed the child and youth epidemiological studies, and found that bipolar rates fell close to zero, when concordance of parental and youth report was required for diagnosis. It was unclear if any pre-pubertal children were diagnosed with bipolar disorder across 12 epidemiological studies using strict criteria. Bipolar rates rose when there was only a youth informant, and impairment criteria were not included.

The methodologically best study found a lifetime prevalence of bipolar-I and bipolar-II disorder of 0.1% with parent and child/youth concordance, all cases being at least 16 years old. With regard to bipolar-not otherwise specified (NOS), the parent report rate was 1.1% and the youth report rate was 1.5%; however, the correlation was no better than chance ($k = 0.02$), and the authors commented that bipolar-NOS appeared unrelated to bipolar-I or bipolar-II. They suggested the term 'mood lability' might be more appropriate (Stringaris et al., 2010: 36).

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. Further research is required on illness trajectories among well-defined types of bipolar disorder before definitive models can be developed for staging the course of the illness (Duffy and Malhi, 2017). This research may lead to

soundly based models of early detection and early intervention. Meanwhile, as Duffy and Malhi suggest, we should take careful aim before 'firing' at phenomenology that may or may not be implicated in the illness trajectories.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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Adolescents who seek help for depression report greater lifetime use of alcohol and increased experience of alcohol-related problems

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DOI: 10.1177/0004867418763539

To the Editor

Recently, Sheppard et al. (2017) reported that almost 60% of Australian adolescents with unmet psychological needs use alcohol or other drugs as a self-management strategy. Given that young people experience a number of barriers to help-seeking, including the belief that they can resolve the problem by themselves, it is likely that when young people do present for help with psychological problems, many will have experienced alcohol-related harm. We examined help-seeking for depression in a sample of 1884 high-school students (47.6% male, mean age = 15.9 years, standard deviation [SD] = 0.6 years), as well as alcohol use and problems (Lubman et al., 2016). Participants reported lifetime alcohol use, associated adverse outcomes over the past 6 months, and whether they had sought help, either from informal sources (e.g. parents, friends) or health professionals (e.g. doctors, psychologists). It was anticipated that there would be a relatively low incidence of alcohol misuse given the age of the sample, so seeking help from different sources were collapsed into a dichotomous help-seeking (yes/no) variable.

In total, 247 participants (12.8%) had sought help for depression by the 12-month follow-up. Participants who had also sought help for alcohol or other drug use problems ($n = 30$; 1.6%) were excluded. There was a significant association between seeking help for depression and (1) lifetime alcohol use ($\chi^2 = 36.411$, $p < 0.001$) and (2) alcohol-related problems ($\chi^2 = 9.421$, $p = 0.009$; Table 1).

The results indicate that alcohol misuse is prevalent among adolescents who seek help for depression. Indeed, over a third of participants reported consuming three or more separate types of alcohol-related problems over the study period. This is of concern as early, untreated alcohol problems are associated with poorer long-term clinical outcomes, and previous research has identified that general practitioners and mental health professionals do not readily identify co-occurring alcohol misuse among young people presenting with depression (Lubman et al., 2007). Our findings support the notion that routine screening for alcohol misuse should be standard for all young people presenting with psychological problems, given consuming alcohol or other drugs is such a common self-management strategy (Sheppard et al., 2017). In addition, it is critical that treatment for depression in young people highlights the harms associated with alcohol and drug use as a self-management strategy and focuses on the development of alternate coping strategies.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Table 1. Association between seeking help for depression and alcohol use and problems.

	Lifetime alcohol use				Recent alcohol-related problems		
Sought help	Never (%)	<10 times (%)	10–39 times (%)	40+ times (%)	None (%)	1–2 (%)	3+ (%)
Yes	83 (34.4)	101 (41.9)	45 (18.7)	12 (5.0)	45 (42.5)	25 (23.6)	36 (34.0)
No	877 (53.4)	534 (32.5)	158 (9.6)	74 (4.5)	272 (58.7)	83 (17.9)	108 (23.3)

Child and Adolescent Mental Health

Child and Adolescent Mental Health 23, No. 1, 2018, pp. 14–22 doi:10.1111/camh.12231

'Paediatric bipolar disorder' rates are lower than claimed – a reexamination of the epidemiological surveys used by a meta-analysis

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Background: 'Paediatric bipolar disorder' (PBD) is a controversial diagnosis where often prepubertal children as well as adolescents, who may have a range of psychiatric disorders or symptoms, are diagnosed with a severe mental illness requiring lifelong medication. Clinically, it has often been applied in the United States but rarely in most other countries. A meta-analysis (Van Meter et al., Journal of Clinical Psychiatry, *2011, 72, 1250) claimed that the prevalence of PBD was similar to adults at 1.8% with no difference between the United States and other countries. This conclusion has been highly cited.* **Methods:** The heterogeneous nature of the original 12 epidemiological surveys warrants a qualitative analysis, rather than statistical meta-analysis as performed by Van Meter et al. (Journal of Clinical Psychiatry, *2011, 72, 1250). Thus, the meta-analysis and each of the 12 studies (six from the United States; six from other countries) were reexamined.* **Results:** Most of the 12 surveys predated the emergence of the PBD hypothesis. The 12 surveys were mainly of adolescents and at times young adults with few prepubertal children. Prevalence rates in the 12 studies suggest a lower rate of bipolar disorder, especially in non-US samples. For example, the Van Meter et al. (Journal of Clinical Psychiatry, *2011, 72, 1250) meta-analysis 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. Indeed, it could be argued that four of the non-US studies show 0% rates of PBD.* **Conclusions:** Rates of PBD were generally substantially lower than 1.8%, particularly in non-US surveys, and if both parent and adolescent reports were required to meet the diagnostic threshold they fell to close to zero. The reanalysis suggests that bipolar disorder is rare before the expected age of onset in later adolescence.

Key Practitioner Message

- A highly cited meta-analysis of the epidemiological studies covering 'ages 7 to 21-years-old' concluded that PBD was equally prevalent in the United States and elsewhere at 1.8%, suggesting PBD may be underdiagnosed and undermedicated outside the United States.
- Our reexamination of the original 12 community epidemiological surveys reveals few studies included children, heterogeneous methodology unsuited to statistical meta-analysis, and lower rates of bipolar disorder especially outside the United States.

Keywords: Bipolar disorder; epidemiologic studies; nosology; paediatrics; meta-analysis

Introduction

Paediatric bipolar disorder (PBD) was first delineated in two 1995 articles, published in the Journal of the American Academy of Child and Adolescent Psychiatry (Wozniak et al., 1995) and the Journal of Affective Disorders (Geller et al., 1995). This was a significant departure from the traditional concept of mania being exceedingly rare before a peak age of onset in late adolescence to young adulthood. PBD proved to be controversial because it led to many US prepubertal children with significant internalising and externalising symptoms being reconceptualised as having a severe adult mental illness requiring lifelong medication often using complex polypharmacy with drugs that have not been fully trialled for children, rather than with more traditional paediatric diagnoses such as attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder, posttraumatic stress disorder, reactive attachment disorder and other child focused disorders.

US child psychiatry researchers postulated that the clinical picture of bipolar disorder in childhood differed from classical DSM or ICD descriptions of mania and hypomania. Geller et al. (1995) at Washington University in St Louis described cases of 'ultradian' cycling of mood in children where episodes could occur several times per day. While Wozniak, Biederman et al. (1996) at Harvard University postulated in a series of articles that 'juvenile' mania involved chronic irritable mood with 'affective storms' and 'severe temper outbursts,

Published by John Wiley & Sons Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main St, Malden, MA 02148, USA

doi:10.1111/camh.12231

poor concentration and impulsivity with or without clear episodicity'. Both groups' clinical cohorts were predominantly prepubertal children.

By 2004, the interpretation of the DSM criteria initially espoused by these two main US research groups had been translated into widespread clinical practice within the United States to the extent that PBD had become the most common diagnosis in preteen US psychiatric inpatient units (Blader & Carlson, 2007). The diagnosis was not without controversy even within the United States (Moreno et al., 2007), and in most other nations the prepubertal onset of classic bipolar disorder continued to be seen as exceedingly rare. For example, the discharge rates for 5–9-year-olds were found to be 100-fold to 1000-fold or greater in the United States than elsewhere. Rates per 100,000 of population were: United States 27, New Zealand 0.22, Australia 0.14, Germany 0.03 and England 0.00 (Clacey, Goldacre, & James, 2015). The modified criteria of both ultradian cycling and chronic irritability for PBD extended in the United States to adolescent cohorts as well, with adolescent inpatient rates of bipolar disorder in the United States also vastly higher than international rates (Clacey et al., 2015).

In this context, Van Meter, Moreira, and Youngstrom (2011) analysed 12 epidemiological studies: six US and six non-US studies, using meta-analytical statistical methods. They reported a prevalence rate of PBD of 1.7% for the US studies and 1.9% for the non-US studies (Table 1) and concluded:

> 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 paediatric 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).

Germane to this question is what constitutes 'paediatric'? The term PBD is inconsistently used, applying either to prepubertal children or to encompass children and adolescents under the age of 18 years. Van Meter et al. (2011) noted that the vast majority of the 16,222 subjects in the dozen epidemiological surveys were over age 12:

> The fact that few studies included youth under the age of 12 years limits our knowledge of the rate of bipolar disorder in children. Diagnoses in prepubescent children are particularly controversial. (p. 1255).

Despite this caveat, this meta-analysis has been widely cited to support the contention that PBD prevalence for both 'children and adolescents' (e.g. Youngstrom, Jenkins, Doss, & Youngstrom, 2012) and including 'preschool children' (Diler & Birmaher, 2012) is similar around the globe at about 1.8%.

The meta-analysis was critiqued by Carlson and Klein (2014) who noted the epidemiological surveys mainly studied adolescents and did not focus on the prepubertal age range in question, the meta-analysis combined parent and youth data even though there was almost complete disagreement, and did not include follow-up data to validate or invalidate a bipolar spectrum disorder diagnosis. However, Van Meter et al. (2011) continue to be widely cited, and this paper expands on the critique of Carlson and Klein by reexamining the key findings of the 12 surveys. In doing so, further limitations of epidemiological surveys for bipolar disorder in youth are revealed. [Correction added on 1 August 2017, after first online publication: On the first sentence of the Introduction section, the reference of Geller et al., (1995) has been corrected.]

A reanalysis of the 12 studies used in the Van Meter et al. 2011 meta-analysis

These 12 epidemiological studies used heterogeneous methodologies (see Table 1) in terms of: ages of subjects (most studies were of adolescents, not prepubertal children); instruments used; informants (parent, or adolescent/child or both); differing time frames (point, 6-month, 12-month, lifetime prevalence); and the diagnoses considered (mania, hypomania, bipolar-I, bipolar-II, bipolar-NOS, bipolar spectrum disorder BPSD and cyclothymia). Most importantly, the authors acknowledged the limitations in interpreting the wide range of atypical bipolar diagnoses:

> Additionally, incomplete reporting of diagnostic criteria and comorbid disorders made it impossible to assess differences between the 'narrow' (elated or grandiose), the intermediate DSM phenotype, and the broad spectrum model of bipolar disorder or to explore the impact of frequently comorbid disorders, such as attention-deficit hyperactivity disorder, on findings. (p. 1255)

Given the heterogeneity of the 12 studies, it is debatable whether they lend themselves to statistical meta-analysis. As the Cochrane Handbook for Systematic Reviews of Interventions (Deeks, Higgins, & Altman, 2011) notes:

> 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. (Part 2, 9.1.4).

Hence, the current review outlines the findings of each of the 12 studies separately.

The six non-US studies

Kim-Cohen et al. 2003 (conducted 1985, New Zealand). The New Zealand article (Kim-Cohen et al., 2003) concerned 973 11-15-years-olds from the Dunedin longitudinal birth cohort study of 1037 New Zealanders born in 1972/3. Research psychiatric diagnoses have been made at ages 11, 13, 15, 18, 21, 26, 32 and 38 years, with an overall retention rate of 96%. The structured diagnostic interview instrument used for DSM diagnoses was the Diagnostic Interview Schedule (DIS) at 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 traditional view of bipolar disorder.

The article of Kim-Cohen et al. (2003) 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 to compare in a 'follow-back' analysis.

By age 26, 48.2% of the cohort met criteria for a 1-year prevalence of a DSM-IV diagnosis. There had been 29

Table 1. The 12 epidemiological studies

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 months 18	Did not ask about mania till age	1.8%	0% or N/A	0% or N/A	
Verhulst et al. (1997) *N* = 780	The Netherlands 1993 DSM-III-R	DISC 6 month 13–18 years	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 years	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 years	Parent and adolescent agreement required or clinician judgment if nonagreement	0%	0%	0%	
Benjet et al. (2009) *N* = 3005	Mexico City 2005 DSM-IV	CIDI 12 months 12–17 years	Adolescent only informant BD-I % deduced from Benjet et al. text	2.5%	2.05%	2.5%	
Stringaris et al. (2010) *N* = 5326	United Kingdom 2007 DSM-IV	DAWBA Lifetime 8–19 years	Child/adolescent and parent informants with minimal correlation: κ 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	

(continued)

doi:10.1111/camh.12231

Table 1. (continued)

Source Subjects	Location Year completed Criteria	Instrument Prevalence period Age	Critique	Van Meter meta-analysis	BD-I %	Total Bipolar Spectrum %
US studies (Van Meter et al. total = 1.7%)						
Kashani et al. (1987) *N* = 150	Missouri 1986 DSM-III	DICA Lifetime 14–16 years	One girl diagnosed by parent and adolescent agreement and consideration of impairment criteria. Carlson and 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* = 1709	Oregon 1988 DSM-III-R/DSM-IV	K-SADS Lifetime 14-18 years	Adolescent only informant Hypomania and cyclothymia reported BD-NOS cases of 5.7% did not continue as bipolar cases on young adult follow-up	6.7%	0.1%	1.0%
Costello et al. (1996) *N* = 1015	Nth Carolina 1994 DSM-III-R	CAPA 3 month 9–13 years	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 years	Adolescent only informant Do not distinguish what % is mania versus hypomania	1.5%	Part of 1.4%	'Mania-hypomania' 1.4%
Gould et al. (1998) *N* = 1285	United States 1996 DSM-III-R	DISC 6 months 9–17 years	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	United States 2003 DSM-IV	K-SADS, CIDI Lifetime 13–17 years	Adolescent only informant	6.3% (K-SADS)	0.5% (K-SADS) 1.0% (CIDI)	6.2% (K-SADS) 6.6% (CIDI)

cases of mania including three cases who did not meet research criteria but who had been treated by their own doctors for it. 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, McGee, Nadja-Raja, & Williams, 1994) and age 15 and 11 (McGee et al., 1990). Diagnoses were based on the DISC-C if corroborated by parent-report and severity measures. Contrary to the conclusions of Van Meter et al. (2011), Kim-Cohen et al. (2003) stated: 'Diagnoses of manic episode and schizophrenia were not obtained at juvenile ages' (p. 710).

So rather than 1.8% as interpreted from this study by Van Meter et al. (2011) (Table 1), a paediatric rate of 0% for bipolar disorder could be consistent with the results from the New Zealand study or more accurately the data are not detailed enough to derive a figure (Table 1).

Interestingly, prior diagnoses in those with bipolar-I at age 26 included conduct disorder/oppositional defiant disorder (CD/ODD) and juvenile depression. Moreover, these adults with mania histories were less likely than adults without mania to have had a childhood ADHD diagnosis, which is the opposite of the very high comorbidity with ADHD that proponents of broad phenotype PBD claim.

Verhulst et al. 1997 (conducted 1993, the Netherlands). The Dutch study (Verhulst, van der Ende, Ferdinand, & Kasius, 1997) did not assess PBD among prepubertal children. It included 780 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 et al. (2011) quote the highest figure reached in the study's methodology – that of 2.8% having bipolar-I or -II disorder (Table 1).

However, the Dutch study actually indicated a rate of 0% if parent and adolescent responses were correlated for agreement rather than summated (Table 1). On parent interview, 21.8% of adolecents 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. Verhulst et al. discussed these aspects e.g.

> 'Evidently, although the prevalences 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 showed the most impairment.' (p. 335).

Canals et al. 1997 (conducted 1994, Spain). The Spanish study (Canals, Domenech, Carbajo, & Blade, 1997) also did not include prepubertal children. It used the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), to interview 290 17–18-year-old adolescents for point prevalence of psychiatric disorders. They found by ICD-10 criteria 29.3% to have a current psychiatric disorder. There was a 2.4% rate of hypomania by ICD-10 criteria but 0% rate by DSM-IIIR criteria and nil cases of mania by either criteria (Table 1). Van Meter et al. (2011) chose to use the ICD figure from Canals et al. (1997) (Table 1) 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.

Lynch et al. 2006 (conducted 2002, Republic of Ireland). The Irish study (Lynch, Mills, Daly, & Fitzpatrick, 2006) surveyed 723 12–15-years-old youth in urban Dublin schools and found no cases of bipolar disorder (Table 1). 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: 'interviews with parents and child are combined and where there is disagreement . . .the interviewer makes a clinical decision regarding diagnosis or not.' (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 noncompletion of consent forms.

Benjet et al. 2009 (conducted 2005, Mexico). The Mexican study (Benjet, Borges, Medina-Mora, Zambrano, & Aguilar-Gaxiola, 2009) also included children as young as 12. They interviewed 3005 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 (Table 1). They acknowledged the very high rate of overall psychiatric disturbance and postulated that rapid globalisation, urbanisation and other psychosocial stressors in Mexico City could be contributory.

Stringaris et al. 2010 (conducted 2007, United Kingdom). The UK study (Stringaris, Santosh, Leibenluft, & Goodman, 2010) was a follow-up study of the British Child and Adolescent Mental Health Survey

doi:10.1111/camh.12231

(B-CAMHS04). It involved a sample of 5326, 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 (National Institute for Mental Health). Because of the controversy over early-onset bipolar disorder that was becoming known 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 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 that quoted by the Van Meter et al. (2011) meta-analysis. Stringaris et al. quoted the overall rate for bipolar-I and bipolar-II as a lifetime prevalence of 0.1% (Table 1).

There was a 10-fold increase however with regard to subthreshold bipolar-NOS cases where manic symptoms lasted between hours and 3 days – 1.1% by parent report and 1.5% by youth report. There were significant comorbid disruptive behaviour disorders particularly with the parent-report group and with disruptive behaviour disorders and anxiety disorders with the self-report group. Reflecting the findings in the Dutch study, the two groups were different, the correlation between parent and youth report was no better than chance, 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 disorders was the valid finding, Van Meter et al. (2011) reported an overall lifetime prevalence of bipolar spectrum disorders from this study as 1.2%, which would seem to be the bipolar-I and bipolar-II group plus the parent-reported bipolar-NOS group (Table 1).

The six US studies

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 sample was 150 adolescents (75 boys, 75 girls) aged 14–16-years-old, interviewed on home visits with the Diagnostic Interview for Children and Adolescents–Child Version (DICA-C) and parents with the DICA–Parent Version (DICA-P) as well as parents completing the Child Behaviour Checklist amongst a range of other questionnaires. Although information from the DICA-P was 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 point prevalence of psychiatric disorder was 18.7% (28 adolescents). While adolescent reports of manic symptoms were frequent at 13.3% (Carlson & Kashani, 1988), they did not meet impairment criteria and only one adolescent girl (0.7% of the total sample) was considered to have mania in Kashani et al. (1987) corroborated by her parent (Table 1). Three adolescents (2%) had a major depression as well as manic symptoms and may have had cyclothymia (Carlson & Kashani, 1988).

Lewinsohn et al. 1995 (conducted 1988). Lewinsohn, Klein, and Seeley (1995) reported on the Oregon Adolescent Depression Project (OADP). The study did not assess PBD among prepubertal children. In their survey of 1709 adolescents aged 14–17-years-old, repeated for 1507 at 1 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%; Table 1). In addition Lewinsohn et al. (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.' 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).

But in fact that work was later published by Lewinsohn et al. themselves. A large proportion (81%) of the original cohort was reassessed 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 ($n = 97$ originally 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, 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 Lewinsohn study (1995) is 0.1% and of bipolar spectrum disorders, 0.9%.

Costello et al. 1996 (conducted 1994). As reported by Van Meter et al. (2011), the Great Smoky Mountains study of 1015 9–13-year-old children (Costello et al., 1996), found a 3-month prevalence rate of 0.10% of hypomania and nil cases of mania (Table 1). 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 they broke down disorders

under disruptive behaviour, depressive disorder, anxiety disorder and substance use disorder categories. [Correction added on 13 September 2017, after first online publication: The year of the second citation of Costello et al. in this paragraph has now been corrected to '2003'.]

Andrade et al. 2006 (conducted 1994). Andrade et al. (2006) did not assess any preteen children; it 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% (Table 1). There was no elaboration on the subject of mania/bipolar disorder in the article. Van Meter et al. (2011) report the figure as 1.5% (Table 1).

Gould et al. 1998 (conducted 1996). Gould et al. (1998) surveyed 1285 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 (Table 1). 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 et al. (2011) quoted it as 1.3% (Table 1). The text of Gould et al. (1998) reports diagnoses of 'hypomania' as well as 'mania' made, but only 'mania' 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 by time of interview'. But in a table they list two age ranges of '7–12 years' and '13–18 years'. Van Meter et al. (2011) thus cite the age range as '7–18 years'.

Kessler et al. 2009 (conducted 2003). Kessler et al. (2009) also did not assess any preteen children; it reported on structured interviews with a representative sample of 347 13–17-years-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 adolescent and parent. The timing of this study coincided with growing popularity of the PBD diagnosis and the authors were keen to ascertain the 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% (Table 1). 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.

Discussion

Marked discrepancies between international and US surveys

The furore over 'paediatric bipolar disorder' really focuses on whether the condition usually considered to onset in late adolescence and young adulthood has been missed and, in fact occurs more frequently in children below age 12 than heretofore thought, requiring the prescription of medication for bipolar disorder amongst children before puberty. The meta-analysis by Van Meter et al., which addresses mostly adolescents, contends that the overall rate of bipolar spectrum (spectrum, not just mania) is about 1.8% and the same worldwide. However, a reexamination of the studies that comprise the meta-analysis reveals that rates of bipolar-I in the United States are quite low (0.0%–1.0%) with understandably higher rates for bipolar spectrum (up to 6.7%) depending on how that is defined.

Outside the United States, rates are perhaps even lower (0.0%–0.1%), except in Mexico (Benjet et al., 2009: 2.05%) for mania. In particular, a careful UK study, Stringaris 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 methods differences, especially informant differences. 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 but the issue is not straightforward (De Los Reyes et al., 2015). Parent/caregiver report has been claimed to have advantages over adolescent report in diagnosing youth with PBD (Youngstrom, Genzlinger, Egerton, & Van Meter, 2015), hence the adolescent-only reports in the United States, Mexican and Spanish studies may explain their findings of higher bipolar spectrum disorder rates.

There are also markedly divergent views amongst researchers on what constitutes bipolar disorder in the paediatric age group. This is an issue for the adult population as well. These views, described as 'liberal' and 'conservative' perspectives bedevil the field (Carlson & Klein, 2014). Bipolar disorder, outside of florid euphoric manic episodes fulfilling DSM-5 duration criteria, is very much in the eye of the beholder. This was highlighted in a transatlantic comparison study of child psychiatrists' diagnosing practices in five written clinical vignettes. In that study, US child psychiatrists were significantly more likely to diagnose mania in three out of the four complex cases, while British child psychiatrists only diagnosed the single classical manic episode vignette at a comparable rate to their US colleagues (Dubicka, Carlson, Vail, & Harrington, 2008).

Most surveys did not include prepubertal children

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. (1995)'s original cohort of 43 children were under age 12. Subsequent studies by that group include drug trials of 4–6-year-old children (Biederman et al., 2005). 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), 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 et al. (2011) are significantly older than these PBD research cohorts. They are not typical of the large number of children diagnosed with bipolar disorder on preadolescent US psychiatric inpatient units (Blader & Carlson, 2007). As Van Meter et al. (2011) note:

> Given questions regarding the role of puberty in the onset of mood disorder, the assessment of participants' pubertal stage would contribute valuable information to the field. (p. 1255)

Conclusion

The meta-analysis of 12 community epidemiological surveys of mainly adolescent youth conducted by Van Meter et al. (2011) found a dozen studies of interest. However, the heterogeneous nature of these 12 studies does not lend themselves neatly to a statistical meta-analysis. 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 methodology correlated parent and child reports for agreement, and included impairment criteria, that rates of bipolar-I disorder in children and adolescents were close to zero outside the United States and only slightly higher in the United States, though rates of bipolar spectrum disorder were slightly higher. Articles that cite the meta-analysis need to critically examine the original studies.

Acknowledgements

The authors would like to acknowledge the late Mickey Nardo of Emory University, Atlanta; Ed Levin of Alta Bates Medical Center, Berkley; and Anja Kriegeskotten of Northside Child & Youth Psychiatry, Brisbane for their reading and comments on the manuscript. The authors declare that they have no competing or potential conflicts of interest.

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Accepted for publication: 6 June 2017
Published online: 17 July 2017

Debate

ANZJP

Australian & New Zealand Journal of Psychiatry
2019, Vol. 53(6) 499–500
DOI: 10.1177/0004867418797419

Can antipsychotic medication administered for paediatric emotional and behavioural disorders lead to brain atrophy?

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In recent years, there has been considerable debate in adult psychiatry as to whether antipsychotic medication can cause cerebral atrophy, based on the findings of animal and human studies. However, the possibility that antipsychotics might have long-lasting effects on the structure and function of the developing brain has been less widely discussed in child psychiatry, despite the rising prescription rates of antipsychotics among Australian children and adolescents. A recent survey of Australian paediatricians found that psychotropics were the most commonly prescribed class of medication in paediatric practice. Although stimulants were the most prescribed psychotropic medication, antipsychotics were prescribed to 5.6% of children with developmental-behavioural and mental health diagnoses (Efron et al., 2017).

It is well recognised that children are more sensitive than adults to the side effects of second-generation antipsychotics (SGAs), such as obesity, diabetes and sedation. However, there are no published studies on the possible effects of antipsychotic exposure on the brain volumes of children and adolescents treated for non-psychotic disorders. At present, our only guides are studies of adult patients with psychotic disorders, and animal studies that indicate cerebral atrophy can occur in the brains of normal juvenile animals exposed to antipsychotics (Vernon et al., 2011).

Evidence from animal studies indicates that antipsychotic induced cerebral atrophy might occur in adult and juvenile animals in the absence of any neurological disease process like schizophrenia. For example, macaque monkeys demonstrated significant total brain weight loss of approximately 10% after 17–27 months of exposure to haloperidol or olanzapine, compared to macaque monkeys receiving sham medication (Dorph-Peterson et al., 2005). All major brain regions were affected, but the most significant changes were noted in the frontal and parietal lobes.

A juvenile rat study replicated these findings with significant decreases in whole brain volume loss of between 6–8% following just 8 weeks of exposure to either haloperidol or olanzapine, compared to sham medication (Vernon et al., 2011). Most of the volume loss was identified in the frontal cerebral cortex. Of note, the effect was of similar magnitude for both the first-generation antipsychotic, haloperidol and the SGA, olanzapine.

It is well known that patients with schizophrenia experience progressive brain volume loss. These findings reinforced the hypothesis that schizophrenia is potentially a neurodegenerative illness. However, based on animal studies, it has also been postulated that some of the progressive brain volume loss seen in schizophrenia might be a direct effect of antipsychotic medication.

In a landmark study, Ho et al. (2011) specifically investigated the potential for antipsychotic associated brain volume loss. This cohort study followed up 211 patients with first episode schizophrenia using sequential high-resolution magnetic resonance imaging (MRI) scanning (average of three scans) over an average of 7.2 years. The study found that greater intensity of antipsychotic treatment (doses and treatment length) was associated with a small but significant loss of total brain volume. This effect remained, even after controlling for illness duration, illness severity and substance abuse. In fact, illness severity had only a modest correlation with total brain volume loss. The authors commented that these

> *findings may lead to heightened concerns regarding potential brain volume changes associated with the sharp rise in atypical antipsychotic use in non-schizophrenia psychiatric disorders. Even though no studies have assessed the long-term effects of antipsychotics on brain volumes in nonschizophrenia patients, our results suggest that antipsychotics should still be used with caution in these*

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patient groups after careful risk-benefit assessment. (p. 135)

Nevertheless, SGAs are being prescribed for large numbers of children and adolescents with non-schizophrenic disorders, despite limited study of their safety and efficacy. The practice began over a decade ago in the United States, and according to industry data from Intercontinental Marketing Services (IMS) Health, antipsychotics were being widely prescribed for US children and adolescents by 2006 (42,459 children aged 1–6 years; 220,305 aged 7–12 years and 305,165 aged 13–18 years: Olfson et al., 2015). Rates for the youngest cohort were roughly 15% higher in 2008 before falling by around 25% by 2010, following new pre-authority prescribing laws. Adolescent rates continued to climb.

The leading diagnostic groups, for which SGAs were prescribed in the United States, were boys with autistic spectrum disorder or disruptive behaviour disorders including attention-deficit hyperactivity disorder, oppositional defiant disorder and conduct disorder. SGA prescription rates had also risen for 'paediatric bipolar disorder', a controversial diagnosis, distinct from classical bipolar disorder, and diagnosed on the basis of affective lability or irritability. In the IMS Health data, 8% of scripts for 1–6 year olds were for bipolar disorder, as were 13% of scripts for children aged 7–12% and 20% of scripts for adolescents aged 13–18 (Olfson et al., 2015). Prescriptions for paediatric bipolar disorder included multiple psychotropics over many years, sometimes with more than one SGA concurrently.

While there was a rise in SGA prescription rates for non-psychotic child and adolescent mental health diagnoses in the United States, Olfson and colleagues noted that *most young people treated with antipsychotics did not have any diagnosis recorded in their health care claims data* (p. 872). SGAs were often used as a stand-alone treatment behavioural problem with less than a quarter of the children and adolescents prescribed SGAs receiving any form of psychosocial therapy.

With recent evidence that antipsychotics are now being more widely prescribed for Australian children and adolescents (Efron et al., 2017), there is an urgent need for human studies on the possible effects of SGAs on the structure and function of the developing brain, including whether SGAs might be neurotoxic, leading to cerebral atrophy, as found in studies of juvenile animals. Pending this research, psychiatrists and paediatricians should be even more cautious about prescribing SGAs for non-psychotic disorders (Ho et al., 2011). If SGAs are being considered as part of a comprehensive treatment plan for a severe developmental-behavioural or mental health disorder, doctors need to inform parents and young people about the recognised side effect profile, including the risk of substantial weight gain. In addition, the recent findings on brain volume loss following antipsychotic administration in the juvenile animal studies indicate that doctors should also discuss with parents and young people whether there might be any potential risks for the developing brain.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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DOI: 10.1111/bdi.12692

DEBATE

WILEY BIPOLAR DISORDERS

Lacunae in the evidence for pediatric bipolar disorder: A response to the ISBD Task Force Report

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1 | INTRODUCTION

The International Society for Bipolar Disorders (ISBD) has released a Task Force Report (TFR) that details the research into pediatric bipolar disorder (PBD).[1] The TFR suggests a high prevalence for the PBD phenotypes in community samples around the world (2.06% of children and youth aged 7–21 years). The prevalence estimate suggests that millions of young people could have early forms of bipolar disorder (BD) that require combined pharmacologic and psychosocial treatment. This claim deserves further discussion and debate, as it has major implications for world psychiatry.

Pediatric bipolar disorder is controversial, especially the treatment of BD among prepubertal children.[2] While early intervention for BD may prove effective in reducing long-term morbidity, the level of evidence needs to be very high, because the benefits have to outweigh the known harms of false positive diagnoses of BD in childhood. These harms include the serious side effects from the long-term use of BD medications such as second-generation antipsychotics (SGAs) for children who are incorrectly diagnosed with BD; the psychological effects of inaccurately labeling children with a severe lifelong mental illness; and overlooking alternative causes for mood lability in childhood. Our article critically examines the evidence presented for the PBD phenotypes, questions the TFR's interpretations, and proposes new studies to fill lacunae in the research.

The central question is whether BD begins with the phenomenology proposed for PBD. The longitudinal high-risk bipolar offspring studies provide the best evidence on this question. Unfortunately, the TFR does not systematically review the bipolar offspring studies, however, Duffy and Malhi recently concluded, "the early course of bipolar disorder charted from prospective studies of high-risk offspring is strikingly different from that derived from studies of clinical samples of children diagnosed with paediatric bipolar disorder" (p. 761).[3] Bipolar offspring who later develop BD may experience childhood sleep and anxiety disorders, but do not have brief prepubertal manic episodes, and the comorbidity with externalizing disorders that characterize the PBD phenotypes.

Most bipolar offspring studies find that mania is rare before puberty, and BD usually begins from mid-adolescence with a depressive episode.[3] The TFR mentions the Pittsburgh and Dutch bipolar offspring studies (TFR: Ref. 50), but does not discuss the intriguing differences in the age of onset for mania/hypomania. The USA study is unusual in finding an early age of onset for mania/hypomania, while the European study is more typical with a mean age of onset for mania/hypomania of 19 years (range 13–31 years), a mean age that may well rise as more adult Dutch offspring develop BD.

Based on the evidence from bipolar offspring studies, it may prove difficult for epidemiological studies to reliably measure the early signs of BD in childhood, because the symptoms are so non-specific (eg, sleep disturbance and anxiety). If this is correct, the default position for epidemiological studies should be measuring the rates of classical mania and hypomania. However, the TFR's 2.06% community prevalence estimate for PBD is based on a broad interpretation of the phenomenology for childhood bipolar spectrum disorders in a meta-analysis of 12 epidemiological community studies (TFR: Ref. 1), updated with six further studies.[1] The prevalence estimate is 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.[4] If the epidemiological studies required parent–child agreement to meet the appropriate diagnostic thresholds, BD-I and BD-II were rare before later adolescence.[4]

In terms of the clinical cohort studies, future research would benefit from taking a more international perspective, given that most PBD research has been USA based. The ISBD Task Force exemplifies the trend: most (14/18) of the TFR's co-authors are affiliated with USA universities with single co-authors from Canada, the UK,

Korea, and the Netherlands.[1] While this clearly demonstrates the major USA contribution to PBD research, international collaborative studies are required to address the disparate diagnostic rates of BD in childhood and youth.

At present, European clinicians are far less likely than USA clinicians to diagnose prepubertal mania, unless faced with clear-cut classical symptoms (TFR: Ref. 23). Comparisons of hospital discharge diagnosis rates find 100 to 900-fold lower rates of pre-adolescent, and 30- to 300-fold lower rates of early adolescent BD diagnoses in European and Australasian countries compared to the USA.[5] BD is either dramatically overdiagnosed among children and youth in the USA or dramatically underdiagnosed in the rest of the world. It is clearly unsatisfactory that children's mental health treatment is determined by their nationality. 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 the 3rd edition of the Diagnostic and Statistical Manual (DSM-III). Further research is required to inform the next edition of the DSM on BD in youth.

Future clinical cohort studies should include systematic examination of the proximal causes of mood lability in childhood and adolescence, as well as putative BD phenotypes. The TFR notes psychosocial factors that can impact on mood such as early adversity, trauma, negative expressed emotion, parental mental illness, parental substance abuse, and parental unemployment, but mostly interprets them as variables affecting the course of BD. However, psychosocial factors such as trauma may cause mood instability. More systematic study should address lacunae in the PBD cohort studies (eg, TFR: Refs. 65, 67, 89, and 90), 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 (TFR: Ref. 64), do not discuss the finding.

Finally, we need better studies of early intervention in BD. These studies should follow from the best evidence on the developmental trajectory. Based on the bipolar offspring studies, the safest course is to reserve BD treatment until an episode of classical mania or hypomania, usually after mid-adolescence. Obviously, alternative forms of mental health treatment are required for the highly distressed children who present with externalizing disorders and mood lability, depending on the likely etiology. Psychosocial treatment, including family support and psychoeducation, is also indicated for high-risk bipolar offspring. Medication is usually not the first or best option for childhood mood lability. SGAs present known health risks, because young people are highly sensitive to the metabolic side effects of SGAs, such as obesity and diabetes.[1] In addition, the long-term benefits of SGAs are unclear, as drug trials are generally short-term, and none demonstrate that SGAs reduce the risk of BD in later life.[1]

In summary, we suggest that further studies are required before the USA practice of diagnosing and treating BD in childhood is widely translated into the mental health care of millions of children and youth in the developed and developing world. It is premature to treat children for putative BD, when we remain unsure of the developmental pathways. Early intervention should follow from a better understanding of the developmental trajectory of the various BD subtypes.[3] Meanwhile, based on the current evidence, the default position should be that BD usually begins after mid-adolescence, but very occasionally classical mania/hypomania can present among older children or younger adolescents, requiring specialist mood disorder treatment.

ACKNOWLEDGEMENTS

The authors acknowledge editing and helpful advice on revising the article from Brenda Jericho.

DISCLOSURES

The authors have nothing to disclose.

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How to cite this article: Parry P, Allison S, Bastiampillai T. Lacunae in the evidence for pediatric bipolar disorder: A response to the ISBD Task Force Report. *Bipolar Disord*. 2018;00:1–2. https://doi.org/10.1111/bdi.12692

Child and Adolescent Mental Health

Child and Adolescent Mental Health 24, No. 1, 2019, pp. 92–94 doi:10.1111/camh.12306

Debate: Bipolar disorder: extremely rare before puberty and antipsychotics cause serious harms – a commentary on Van Meter et al. (2019)

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We are grateful to Carlson (2018), and to Van Meter, Moreira and Youngstrom (this issue) for their commentaries on our narrative analysis of the dozen epidemiological studies of bipolar disorder (BD) in children and youth used in an influential meta-analysis of what is commonly termed 'paediatric bipolar disorder' (PBD) in the United States (Parry, Allison, & Bastiampillai, 2018a). It provides an opportunity to further debate this important and controversial topic. While Van Meter et al. (this issue) state that their meta-analysis 'indicated that bipolar disorder manifested at statistically indistinguishable rates in youth community samples across the world' (p. **), we found that closely examining each of the 12 studies revealed dramatically different rates, due to differences in the definitions of PBD, the heterogeneity of study methods and combining parent and youth reports, even if discrepant. The Van Meter meta-analysis reported a population rate of 1.8% for bipolar spectrum disorder among young people aged 7 to 21-years-old, but the rate is probably far lower, especially for children and younger adolescents.

We completely agree with Van Meter et al. (this issue) that this debate really matters, and that the fundamental issues are 'accurate diagnosis' and 'appropriate treatment' to provide children and adolescents with 'a fair chance at a good quality of life' (p. **). There is often a long delay in diagnosing BD, and clinical vigilance is vital. However, premature and incorrect diagnosis of BD can harm children through: (a) overuse of medications such as antipsychotics, exposing children to adverse effects; (b) labelling, where children and youth and their carers may misinterpret normal or reactive mood lability as BD, and thereby damage the child's sense of self; (c) the missing of other childhood diagnoses such as ADHD; (d) the missing of contextual factors including attachment disorganisation, trauma, family stressors and childhood maltreatment. Most studies of PBD do not consider trauma/maltreatment, or find rates that are lower than usual community prevalence, suggesting that the negative effects of trauma/maltreatment might be underestimated in these studies (Parry, Allison, & Bastiampillai, 2018b).

PBD is diagnosed infrequently outside the United States, which either represents substantial underdiagnosis in European and Australasian countries, or pervasive overdiagnosis in the United States. Hospital discharge diagnosis rates of BD are 100- to 900-fold less in preadolescents and 30- to 300-fold less in young adolescents in the United Kingdom, Germany, Australia and New Zealand than in the United States (Clacey, Goldacre, & James, 2015). A 17-year study of 5483 paediatric psychiatric admissions in the Czech Republic, found only 0.83% of this severe clinical cohort diagnosed with BD, the youngest first manic episode being 11.5-years-old and mean age of first manic episode 15.6-years-old (Goetz et al., 2015). With combined inpatient and outpatient data, a 15-year study from a large English paediatric psychiatric service found only 35 cases of BD out of 3586 patients (0.97%) with mean age of 14.3 years (SD ±2.16) (Chan, Stringaris, & Ford, 2011). An 18-year nationwide register study of all paediatric (<19-years-old) diagnoses in Denmark reported a national population rate of 0.001% in the first half rising to 0.004% in the second half of the study period (Kessing, Vradi, & Andersen, 2014).

Van Meter et al. (this issue) argue in favour of the US practice of treating putative forms of BD in childhood and adolescence, but do not discuss the treatment risks. This remains a central issue. Second-generation antipsychotics (SGAs) are the recommended first-line treatment for acute manic/mixed episodes in children and adolescents, because mood stabilizers such as lithium and anticonvulsants have limited benefit (Goldstein et al., 2017; Parry et al., 2018b). The widespread use of SGAs has been associated with public health risks for US children and adolescents, due to severe weight gain, and the metabolic syndrome. There has been minimal research on the effects of SGAs on the developing human brain, however, cerebral atrophy has been observed in studies of juvenile animals (Bastiampillai, Parry, & Allison, 2018). The known side-effect burden, and potential risk for the developing brain are particularly concerning, given the lack of long-term studies of SGAs used ostensibly to prevent or treat BD in children and younger adolescents.

The main scientific question is whether or not BD frequently begins in childhood and early adolescence. Commenting on the retrospective studies of the age of onset of BD, Van Meter et al. (this issue) referenced the seminal study of Kraepelin as including 'descriptions of prepubertal cases' (p. **). 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 as: 0.4% onset by 10-years-old, a further 2.5% by 15-years-old, another

Published by John Wiley & Sons Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK and 350 Main St, Malden, MA 02148, USA

doi:10.1111/camh.12306

16.4% by 20-years-old, a further 30.7% by age 30. He noted a quarter of all cases by 15-years-old were of the melancholic type, so strictly speaking those could not yet be diagnosed as BD.

Van Meter, Moreira, and Youngstrom (2018) cite two recent articles that explore retrospective recall data to suggest more than half of adults with BD experienced first symptoms by age 21 and 30% before age 13. However, these results are orders of magnitude greater than Kraepelin's findings. There are many recent studies with later ages of onset from retrospective recall. For example, an Australian study of 218 adults with bipolar-1 disorder (BD-I) or schizoaffective disorder (mean 41-years-old) found, while delay from early symptoms to psychiatric treatment was lengthy, the median age of onset of manic symptoms was 21-years-old, and of a diagnosable manic episode was 24.1-years-old (Berk et al., 2007).

The longitudinal study of high-risk offspring of parents with BD is the most robust method of elucidating the age of onset of BD, and the psychopathology that may precede the index manic/hypomanic episode. A review of six offspring studies (Canadian, Dutch, Swiss, US Amish, US University of Indiana/multisite, US University of Pittsburgh) provides a comprehensive summary of these important findings (Duffy, Vandeleur, Heffer, & Preisig, 2017).

In five of the studies 'the index manic or hypomanic episode typically manifests in mid-late adolescence and early adulthood' (p. 7) with nonspecific anxiety and sleep disturbance psychopathology preceding it. Childhood brief hypomanic symptomatology was generally not predictive of later BD though more proximal prodromal hypomanic symptoms did relate to diagnosable BD onset. Duffy et al. concluded: 'manic-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). They found that ADHD, which is commonly highly comorbid in the PBD research cohorts, was unrelated to later BD, though neurodevelopmental disorders had some correlation with later schizoaffective and schizophrenia disorders.

However, Van Meter et al. only cite the Pittsburgh study, not the five other studies that found the age of onset of BD was usually midadolescence or later. Duffy et al. noted that the Pittsburgh study 'stands apart somewhat from these other published studies … 50% had mania prior to age 12 (compared to 0% in other studies)' (p. 6). Carlson (2018) outlined various differences between the Pittsburgh and Dutch studies with greater numbers of stressors potentially contributing to higher rates of non-BD symptoms in the Pittsburgh study. Future high-risk offspring studies need to ensure accurate diagnoses are made of adult probands, as this may be a factor in the discrepant findings.

If the majority of the high-risk offspring studies are correct, it will prove extremely difficult to reliably detect mania/BD-I in epidemiological studies of children and younger adolescents, since the index manic or hypomanic episode rarely occurs before midadolescence. If cases of prepubertal and peri-pubertal mania/BD-I are rare, reliable prevalence estimates could only be made within huge population samples. It will also be difficult to detect prodromal BD in childhood, because the index episode is typically preceded by common nonspecific symptoms such as anxiety and sleep disturbance.

On this basis, the results of the Goldstein et al. (2017) and Van Meter, Moreira, and Youngstrom (2011) meta-analyses are unlikely to be accurate for children and younger adolescents. Their high prevalence estimates of around 2% for bipolar spectrum disorders amongst youth aged 7–21 years suggests that millions of young people around the world have untreated BD (Parry et al., 2018b). However, Van Meter et al. (this issue) acknowledge that there are few epidemiological studies of PBD symptoms in children. In addition, BD-not otherwise specified (NOS) as diagnosed in childhood and adolescence is probably not a variant of adult BD. This was the conclusion of the British epidemiological survey (Stringaris, Santosh, Leibenluft, & Goodman, 2010) that found only one case (0.03%) of BD-I/BD-II among the 8 to 15-year-olds (0.03%), which disappeared if parent–youth agreement required, but a 2.5% rate of BD-NOS for the full 8 to 19-year-old sample. Based on no change in BD-NOS rate by age, a correlation 'no better than chance' between parent and child/youth report, high comorbid externalising symptoms and no recent depressive symptoms, the authors concluded: 'our findings call into question the extent to which BP-NOS in youth really is a variant of DSM-IV BP, superficially similar symptoms may not necessarily imply deeper similarities in aetiology or treatment response' (Stringaris et al., 2010, p. 36).

The more recent Brazilian survey (Pan et al., 2014) cited by Van Meter et al. (this issue) used similar methodology to the British survey to find a 0.2% rate of BD-I/BD-II and 1.6% rate of BD-NOS in 6 to 12-year-olds but, based on latent class analysis, concluded: 'we may have ascertained symptoms of externalising disorders rather than manic symptoms' (Pan et al., 2014, p. 631). Given the comments of these researchers and the findings of the robust longitudinal high-risk off-spring studies, it is more likely that the epidemiological studies are detecting various combinations of severe mood lability and externalising behaviour, from a variety of causes, rather than very early symptoms of adult BD.

Hence, we disagree with Van Meter and colleagues' conclusion (this issue) that the child and adolescent epidemiological studies are suitable for meta-analysis. They argue: 'combining effect sizes from empirical studies using meta-analysis enables us to see the forest from the trees' (p. **). Undoubtedly, this is true if the technique is used appropriately, however, the Van Meter and Goldstein meta-analyses obscure the heterogeneity of study methods, the wide variety of results within each study, differences between parent and youth informants, and the limitations of individual studies, as detailed in our previous article on the measurement issues (Parry et al., 2018a). Meta-analysis may provide misleadingly high prevalence estimates of BD amongst young people, probably because severe mood lability and externalising behaviour with various aetiologies are bundled together as 'bipolar spectrum disorders'. Using the same metaphor, we are then unable to distinguish the many distinct species of trees that make up the 'forest' of childhood mood lability.

Carlson (2018) makes several valuable suggestions for untangling these issues in future epidemiological studies: the use of consistent criteria for BD across

international studies; separate reporting of mania/BD-I versus bipolar spectrum disorder; keeping separate the reports by different informants; treating adolescent reports of 'mania' as suspect, unless corroborated by parent report; and realising that the frequently used semistructured interviews may diagnose 'hyperkinetic conduct disorder' as PBD. We agree with each of these points. In addition, as we have argued, the epidemiological studies should be informed by the emerging evidence on the developmental trajectory of adult BD, otherwise various forms of severe mood lability in childhood and adolescence may be mistaken for the early stages of BD.

We strongly agree with Van Meter et al. that we need 'to recognise the impact of bipolar disorder on young people and to commit commensurate efforts to ameliorating it' (p. **), but we disagree on the age from which this impact becomes evident. The balance of evidence from longitudinal studies of high-risk offspring of parents indicates that BD is unlikely to begin in childhood with atypical manic symptoms. Instead it usually begins with nonspecific anxiety and sleep disorders, and diagnosable mania/hypomania generally does not occur until midadolescence or later. Clinicians need to be wary of the current algorithms for the treatment of PBD as they usually involve prescribing SGAs for children, which can cause serious iatrogenic harms.

Conflict of interest

The authors have declared that they have no competing or potential conflicts of interest.

Ethical information

No ethical approval was required for this article.

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Accepted for publication: 9 October 2018

Article

Clinical Child Psychology and Psychiatry
1–17

DOI: 10.1177/1359104519836700
journals.sagepub.com/home/ccp
SAGE

The geography of a controversial diagnosis: A bibliographic analysis of published academic perspectives on 'paediatric bipolar disorder'

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Abstract

Background: The hypothesis that bipolar disorder presents before puberty with atypical mania has proved to be controversial. Published academic perspectives on the validity of Paediatric Bipolar Disorder (PBD) appear to vary between the United States and the rest of the world.
Methods: We examined the perspectives of articles citing four seminal articles. The citing articles were grouped as either supportive or non-supportive of the PBD hypothesis, and the perspectives of the articles by US authors were compared with those by non-US authors.
Results: There were 787 citing articles commenting on PBD, mostly published in US-based journals. Most authors were affiliated with several US institutions. Among the 624 articles with US authorship, the majority (83%) supported PBD. Of the 163 articles by non-US authors, most (60%) supported the traditional view that bipolar disorders are rare before mid-adolescence. Published academic perspectives in favour of the PBD hypothesis are mostly concentrated in several US institutions.
Conclusion: There is majority support for PBD among citing articles from the United States, whereas the traditional perspective predominates in articles from most other countries.

Keywords

Bipolar disorder, nosology, paediatrics, irritable mood, psychiatric diagnosis, child psychiatry, bibliometric analysis, transcultural psychiatry, early medical intervention

Introduction

Bipolar Disorder (BD) is a serious mental disorder and a recent major review article notes that the 'mean age of onset [is approximately] 20 years [of age]' (Vieta et al., 2018, p. 2). The review further states that

> a 5-year delay in diagnosis from the onset of symptoms has been shown in some studies . . . and a longer duration of untreated illness has been associated with an increased number of suicide attempts and a longer duration of illness. (Vieta et al., 2018, p. 2).

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Therefore, early accurate diagnosis of the index manic or hypomanic episode is of high importance. However, there are also risks from overdiagnosis and misdiagnosis with damaging iatrogenic consequences: first, through the adverse physical effects of inappropriate pharmacotherapy; second, through the adverse psychological effects of labelling; and third, due to the psychosocial causes of mental and behavioural problems being overlooked. The review by Vieta and colleagues (2018) also noted:

> [T]he general adolescence onset (and, in rare cases, before puberty) is now recognized, although there is an ongoing controversy regarding the underdiagnosis versus overdiagnosis of bipolar disorders in children in certain countries (p. 12).

These potential risks and benefits of early diagnosis and treatment are evident with what has been termed 'Paediatric Bipolar Disorder' (PBD). The PBD hypothesis proposed that BD presented with symptomatology atypical to adult BD and could be reliably diagnosed and treated in childhood and early adolescence.

Two 1995 articles in particular launched the widespread academic and clinical interest in PBD in the United States. Geller and colleagues (1995) at Washington University in St Louis hypothesised the 'ultradian' cycling of mood in children when brief manic and depressive episodes rapidly cycled during a day. In the same year, Wozniak et al. (1995) at the Massachusetts General Hospital, a teaching hospital of Harvard University (MGH/Harvard), reported that 16% of prepubertal children referred to their psychiatric clinic had 'a DSM-III-R diagnosis of mania' (p. 867); 98% of them had comorbid Attention Deficit Hyperactivity Disorder (ADHD); and the majority (77%) had chronic (mean duration: 3 years) irritability with no euphoria. Both Geller et al. (1995) and Wozniak et al. (1995) reported the onset of BD in their respective prepubertal cohorts at a mean age of 4 years old. Their seminal articles were foundational to the PBD hypothesis. 'Geller–Wozniak Syndrome' has been suggested as an alternative name for these types of phenomenology and does not carry 'erroneous assumptions about aetiology, associations, treatment and prognosis' (Hazell, 2019, p. 1).

In 1997, the American Academy of Child and Adolescent Psychiatry's flagship journal, the *Journal of the American Academy of Child and Adolescent Psychiatry* endorsed both the PBD constructs by publishing a landmark '10 year review' article, authored by Washington University in St Louis academic child psychiatrists Geller and Luby (1997). A second '10 year review' of PBD was published in 2005 by authors from the University of Illinois and University of Pittsburgh (Pavuluri, Birmaher, & Naylor, 2005). These two major review articles accepted both the models of PBD – the ultradian cycling elevated mood symptom complex (Geller et al., 1995) was linked with full *DSM-IV* criteria for BD to be described as 'narrow-phenotype' PBD and the chronic irritability symptom complex (Wozniak et al., 1995) was described as 'broad-phenotype' PBD.

Some ambiguity in terminology applied, with publications describing chronic 'mania' (Biederman, 1998; Geller, Tillman, Craney, & Bolhofner, 2004; Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003) used interchangeably with 'juvenile BD' (Doyle et al., 2010) and 'PBD'. The second 10-year review cited Leibenluft and colleagues (2003) at the National Institute of Mental Health (NIMH), who sought to clarify and define the subtypes of PBD. Leibenluft et al. (2003) had proposed the following: that only children whose symptoms met full *DSM-IV* criteria for hypomania/mania be categorised as 'narrow-phenotype'; two 'intermediate' phenotypes – one with ultradian or ultra-rapid cycling as described by the Washington University in St Louis group and the other of demarcated 'irritable without elevation' episodes; and finally that the 'broad-phenotype' PBD term be used for the chronically irritable cohorts described by the MGH/Harvard group. Later, Leibenluft and colleagues redefined 'broad-phenotype' PBD as 'Severe Mood Dysregulation' (Baroni, Lunsford, Luckenbaugh, Towbin, & Leibenluft, 2009) that was then adopted into the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*) as 'Disruptive Mood Dysregulation Disorder' (American Psychiatric Association [APA], 2013).

The rationale for the new *DSM-5* diagnosis was to reduce BD diagnostic rates among US children (Fristad et al., 2016). This move indicated significant opposition towards the PBD hypothesis by some prominent academic centres of US child and adolescent psychiatry. A two-day workshop convened at the Hastings Center Bioethics Research Institute in 2010 brought US proponents and critics of the PBD hypothesis together and the published report indicated the divergent views (Parens & Johnston, 2010). The convenors concluded 'the BP label may fit poorly many of the children who have received it over the last decade' (p. 11). They noted that a new diagnosis was required for *DSM-5* to reduce the number of PBD diagnoses made, and the name Temper Dysregulation with Dysphoria was suggested (Parens & Johnston, 2010) but was later changed to Disruptive Mood Dysregulation Disorder.

However, the ultradian cycling 'intermediate' phenotype still was called 'narrow-phenotype' PBD in the second 10-year review of the *Journal of the American Academy of Child and Adolescent Psychiatry* (Pavuluri et al., 2005) and referred to as 'Bipolar-I disorder' in some publications (e.g. Geller, Tillman, Bolhofner, & Zimerman, 2008). Even after the publication of *DSM-5*, 'broad-phenotype' PBD was still being referred to as PBD rather than Disruptive Mood Dysregulation Disorder in some publications (e.g. Wozniak et al., 2017).

Based on the available evidence, most clinicians outside the United States have generally not accepted the proposition that BD commonly manifests before puberty. First, in a trans-Atlantic comparison of diagnosing practices based on five clinical vignettes, UK child psychiatrists generally did not diagnose PBD except in a single vignette with clear-cut symptoms of classical mania in an older child. In comparison, faced with the same five clinical vignettes, US child psychiatrists were significantly more likely to diagnose mania than their UK counterparts in three of the other four vignettes. The data also showed that there was divergence among US child psychiatrists with only a substantial minority diagnosing mania in those three vignettes. Furthermore, there was little cross-national difference in the diagnosis of ADHD in the vignettes (Dubicka, Carlson, Vail, & Harrington, 2008).

Second, the greater tendency to diagnose mania in children by a proportion of US clinicians is reflected in a study examining hospital discharge diagnosis rates of PBD, found to be 100- to 900-fold lower among preadolescents, and 30- to 300-fold lower rates among early adolescents in Europe and Australasia compared to the United States (Clacey, Goldacre, & James, 2015). The authors reported hospital discharge rates per 100,000 population of bipolar spectrum disorders for the 5 to 9 years age group as 27 for the United States and 0.14 (Australia), 0.22 (New Zealand), 0.0 (England) and 0.03 (Germany). Rates for the 10 to 14 years age group were 134 (USA), 3.9 (Australia), 1.3 (New Zealand), 0.48 (England) and 0.46 (Germany). Similar low rates for inpatient diagnoses were found in the Czech Republic (Goetz et al., 2015) and for both inpatient and outpatient children and youth in Denmark (Kessing, Vradi, & Andersen, 2014). These recent studies of diagnosis rates in Europe and Australasia show little to no deviation from older British, European and Australasian studies that found mania/hypomania/bipolar disorder to be rare in adolescence and exceedingly rare or not detected in prepubertal children (Barton-Hall, 1952; Räsänen, Tiihonen, & Hakko, 1998; Sigurdsson, Fombonne, Kapil, & Checkley, 1999; Sourander, 2004; Thomsen, Moller, Dehlholm, & Brask, 1992; Werry & McClellan, 1992).

Prospective studies of high-risk offspring of parents, that is at least one parent had a diagnosis of BD-I, provide a more robust method of detecting BD in children and youth. One such 16-year Canadian study found nearly 14% to be diagnosed with a bipolar spectrum disorder. However, 'there was no case of diagnosable mania or hypomania observed prior to age 15.5 years' (Duffy et al., 2014, p. 125). A review of six international offspring studies (Canadian, Dutch, Swiss, Amish, Indiana University and University of Pittsburgh) concluded that in the first five studies 'the index manic or hypomanic episode typically manifests in mid-late adolescence to early adulthood' (Duffy, Vandeleur, Heffer, & Preisig, 2017, p. 7). In contrast, the sixth offspring study by US researchers at the University of Pittsburgh found 'the mean age of onset of mania/hypomania was

13.4 ± 3.8 years' (Axelson et al., 2015, p. 7). Axelson and colleagues' findings are consistent with the hypothesis of 'intermediate' phenotype PBD cases (i.e. ultradian cycling or brief episodes lasting <4 days) in prepubertal and early adolescent children progressing from BD-Not Otherwise Specified (BD-NOS) to BD-II and BD-I over time.

This brief selection of studies demonstrates that there is a considerable discrepancy between diagnostic rates in clinical practice and findings in longitudinal studies for the number of cases and age of onset of BD in children and youth. In general, it appears that early cases of PBD are diagnosed in substantial numbers mainly in areas of the United States. This international discrepancy, primarily between the United States and other countries, has led to considerable debate about whether the PBD construct for BD in youth and particularly in prepubertal children and early adolescence has validity, or whether the 'traditional' perspective, which appears to be still held outside the United States, is missing early cases of BD (e.g. James et al., 2014; Malhi, 2016; Parry et al., 2015; Post et al., 2017).

Differing academic perspectives may be responsible for these discrepant findings. National variations in academic opinion on PBD might influence which clinical trials are undertaken and subsequent practice guidelines besides predicating higher prescribing rates of drugs such as second-generation antipsychotics with potential negative public health effects. The current bibliometric study examines published academic perspectives on the PBD hypothesis. We expected to find that the PBD hypothesis as presented in four seminal articles (Geller & Luby, 1997; Geller et al., 1995; Pavuluri et al., 2005; Wozniak et al., 1995) had gained greater acceptance in the United States than the rest of the world. We hypothesised that pro-PBD articles would be prevalent in articles from the United States, particularly those by authors who were associated with the four academic centres, and 'traditional' perspectives would be more prevalent in articles from other countries, unless there was collaboration with US researchers with views favourable towards PBD.

Methods

Search for citing articles

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). It allows for the compilation of 'citation trees' of articles that all cite a particular reference article. By combining search results of citing articles for several key articles on a topic, a body of literature pertaining to that topic can be compiled. The database allows for sorting of such a body of articles according to authorship, affiliated institutions of authors, countries of authors, year of authorship, publishing journals and so on. This method of examining literature provides insights into the co-authorship networks and the places of origin of articles for a topic.

In the current study, the *Web of Science* was used to download bibliographic records and construct citation trees for the following four seminal PBD articles: Geller et al. (1995), Wozniak et al. (1995), Geller and Luby, (1997) and Pavuluri et al. (2005).

Categorising perspectives on PBD

Each article was then categorised according to whether the authors (1) accepted the PBD hypothesis, (2) were sceptical of the validity of the PBD hypothesis, (3) held to the traditional view that BD has a late-adolescent to early-adult onset, without overtly expressing scepticism about PBD, (4) wrote about Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder as an alternative descriptor for severe irritability or 'broad-phenotype' PBD or (5) did not write in any obvious way about BD in children or youth but had nonetheless cited one of the four seminal PBD articles.

As a template, five articles typical of each of these five groups were delineated by the authors and are listed in the Online Supplementary Appendix A . Based on this template, all articles were read to

assess perspective on PBD by the lead author. *Web of Science* gives the abstracts for all articles. If the article's perspective was not clear from the abstract, then the original article was read from its source. The articles were then assigned as 'Pro-PBD', 'Sceptical', 'Severe Mood Dysregulation/ Disruptive Mood Dysregulation Disorder', 'Traditional' or 'Not Applicable'. The country of origin and affiliated institution of the authors were then compared with these perspectives.

The full list of citing articles and the assigned perspectives are listed in Online Supplementary Appendix B.

Results

On 27 September 2016, the four articles had the following number of citations: Geller et al. (1995): 196; Wozniak et al. (1995): 474; Geller and Luby (1997): 331; Pavuluri et al. (2005): 189. When the four searches were combined, the total number of citations, including overlapping citations, was 835 articles. Forty-eight articles were excluded, as they were considered 'Not Applicable', leaving a total of 787 citing articles (Table 1).

Journals with citing articles

In all, 52% of the citing articles were published in eight US-based journals. The *Journal of the American Academy of Child and Adolescent Psychiatry*, which has a wide readership among US child and adolescent psychiatrists, dominated the publication of the citing articles (92 articles). A second journal that frequently published on PBD was the *Journal of Affective Disorders* (78 articles), the journal of the International Society for Affective Disorders. Other top journals included *Bipolar Disorders*, the journal published by the International Society for Bipolar Disorders (59 articles); the *Journal of Child and Adolescent Psychopharmacology* (51 articles); the *Journal of Clinical Psychiatry* (41 articles), which is the journal of the American Society for Clinical Psychopharmacology and whose website includes extensive pharmaceutical industry advertising; *Biological Psychiatry* (41 articles) which in 2017 had the sixth highest impact factor of 142 among psychiatry journals; the *American Journal of Psychiatry* (24 articles) which had the fourth highest impact factor in 2017; and *Child and Adolescent Psychiatric Clinics of North America* (23 articles).

Table 1. The top 10 journals for this citation tree search.

Journal	Articles	Percentage out of 787	Country of origin	H index (Impact Factor) 2017
Journal of the American Academy of Child and Adolescent Psychiatry	92	11.7	USA	212 (6.250)
Journal of Affective Disorders	78	9.9	USA	158 (3.786)
Bipolar Disorders	59	7.5	Internat.	113 (4.490)
Journal of Child and Adolescent Psychopharmacology	51	6.5	USA	76 (2.901)
Journal of Clinical Psychiatry	41	5.2	USA	183 (4.247)
Biological Psychiatry	41	5.2	USA	283 (11.982)
American Journal of Psychiatry	24	3.0	USA	318 (13.391)
Child and Adolescent Psychiatric Clinics of North America	23	2.9	USA	62 (1.798)
Canadian Journal of Psychiatry	13	1.6	Canada	99 (3.612)
Development and Psychopathology	13	1.6	USA	151 (4.357)

Affiliated institutions of authors of citing articles

Most authors of the citing articles were affiliated with US-based institutions, with the MGH/Harvard group producing the most articles (Table 2). Biederman, Wozniak and colleagues from Boston continued to publish widely (248 articles from MGH/Harvard) in support of the 'broad-phenotype' PBD hypothesis. The 'narrow-phenotype' PBD hypothesis originally from Geller and colleagues at Washington University in St Louis, Missouri (33 articles) was taken forward with continuing research in the Course and Outcome of Bipolar Youth (COBY) study group of Birmaher, Axelson and colleagues at the University of Pittsburgh, Pennsylvania (57 articles). Among 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 583 citations on Google Scholar (as on 9 October 2017).

The University of Cincinnati (63 articles), Case Western Reserve University (54 articles), Cincinnati Children's Hospital (21 articles) and Ohio State University (21 articles) reflected the work of several authors in Ohio (Kowatch, DelBello, and Findling), who were lead authors in another heavily cited PBD article: 'Treatment guidelines for children and adolescents with BD' published in the *Journal of the American Academy of Child and Adolescent Psychiatry* in 2005 (Kowatch et al., 2005) that had accrued 548 citations (Google Scholar, 9 October, 2017).

Other prominent US research institutions included the University of North Carolina (37 articles), reflecting the work of Youngstrom and colleagues; the 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 included in this list reflect the collaboration between authors (Stringaris and colleagues) at Kings College London with Leibenluft and colleagues at the NIMH regarding Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder; between US author Akiskal (University of San Diego, chief editor of the *Journal of Affective Disorders*) and colleagues at the University of Pisa, Italy; between Canadian PBD researcher Goldstein (University of Toronto) and colleagues at University of Pittsburgh; and between sceptical perspective articles by Duffy and colleagues from Dalhousie University in Nova Scotia, Canada.

Perspectives of the citing articles

The citing articles were sorted according to whether they supported or did not support the PBD hypothesis. Overall, most (74%) citing articles supported the PBD hypothesis (Table 3). The minority (26%) of citing articles that did not support the PBD hypothesis comprised four subthemes: (1) overtly sceptical of the validity of the PBD hypothesis, (2) holding a traditional view that BD has a late-adolescent to early-adult onset but did not overtly express a sceptical perspective about PBD, (3) concerned with Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder as an alternative descriptor for severe irritability/'broad-phenotype' PBD and may or may not be open to considering 'narrow-phenotype' PBD as a valid construct, or (4) seeking consensus. 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 BD in youth; 27 (3%) focusing on Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder; and 4 (0.5%) articles attempting consensus on the subject of BD in children and youth.

The perspectives of articles with US authors were then compared with the articles having only non-US authors (Table 3). There were 624 citing articles with at least one US-based author and 163 citing articles with only non-US authors. Support for the PBD hypothesis dominated among the citing articles with US authors (83% were rated as supporting PBD). In contrast, among the 163 citing articles with only non-US-based authors, a minority (40%) were rated as pro-PBD. Most

Table 2. The institutions with at least 10 citing articles.

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 University of New York Stony Brook	27	
State University 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	

non-US articles took either a traditional (39%) or sceptical perspective (18%). There were traditional-perspective articles from authors in a wide variety of countries (USA, UK, France, Canada, India, Germany, Netherlands, Switzerland, Denmark, Norway, Finland, Australia, Ireland, Spain, Sweden, Austria, Belgium, Iran, Japan, Poland, Taiwan, Tunisia and Turkey). Sceptical-perspective articles were also from authors in many countries (USA, UK, Canada, France, Australia, India, Sweden, Germany and New Zealand).

Most of the non-US articles that supported PBD originated from research groups located at the University of Pisa in Italy; 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; and the University of Istanbul in Turkey. There were three recent pro-PBD articles from South Korea: two of those articles, however, had US co-authors from the University of North Carolina. Beyond these groups, there was little worldwide research on PBD, according to the citing articles.

Table 3. Perspectives of the citing articles of authors with US and non-US affiliations.

	Articles with US authors *n* (%)	Articles with only non-US authors *n* (%)	Total *n*
Supporting PBD	521 (83)	65 (40)	586
Sceptical	40 (6)	30 (18)	70
Traditional	37 (6)	63 (39)	100
SMD/DMDD	22 (4)	5 (3)	27
Consensus	4 (1)	0 (0)	4
Total	624 (100)	163 (100)	787

SMD/DMDD = Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder.

It is notable that many of the articles by US authors were by authors of the original four seminal articles. Therefore, the count of US-based citing articles could be considered inflated by self-citing articles. Articles by authors of any of the original four articles are highlighted in Appendices B1 (US authors only) and B2 (US authors and international authors). They accounted for 262 pro-PBD articles, 2 consensus articles, 1 Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder and 1 'Not Applicable' article. Even after these articles are removed, there remains a majority of pro-PBD perspectives among articles with US authors, but it falls from 83% to 75% (Table 4).

Table 4. Perspectives of the citing articles after excluding articles authored by authors of the four seminal articles.

	Articles with US authors *n* (%)	Articles with only non-US authors *n* (%)	Total *n*
Supporting PBD	298 (75.0)	65 (40)	363
Sceptical	40 (10.5)	30 (18)	70
Traditional	37 (9.0)	63 (39)	100
SMD/DMDD	21 (5.0)	5 (3)	26
Consensus	2 (0.5)	0 (0)	2
Total	398 (100)	163 (100)	561

SMD/DMDD = Severe Mood Dysregulation/Disruptive Mood Dysregulation Disorder.

Timeline of the citing articles

Using *Web of Science*, timelines were produced for citing articles with US authors only (Figure 1); articles co-authored by US and international authors (Figure 2); and articles with only non-US authors (Figure 3). Note that due to the data analysis function in *Web of Science* these figures include the 'Not Applicable' articles too. However, they suggest a progression of articles from the United States to other countries. US citing articles peaked in 2006, the US and international co-authored articles peaked in 2013 and the non-US articles peaked in 2010.

Discussion

As expected, the current bibliometric analysis found that the majority of articles from the United States that cited these four seminal articles accepted the PBD hypothesis, whereas the traditional perspective predominated in citing articles from most other countries. These entrenched differences have implications for clinical practice. Published academic opinion is known to influence the lines

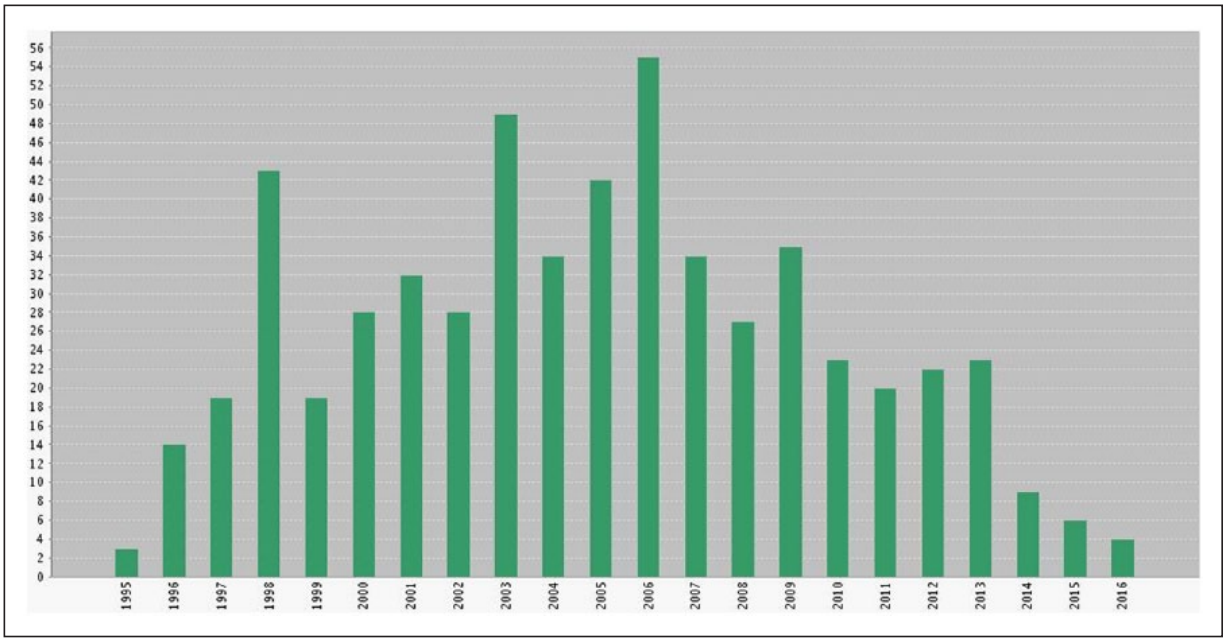

Figure 1. US only citing articles 1995–2016.

of research undertaken and subsequent national treatment guidelines produced. The four seminal PBD articles proposed that PBD was common in US clinical populations and required early diagnosis and treatment. After these articles were published, PBD diagnosis rates increased in the United States, and higher prescription rates of second-generation antipsychotics were noted (Harrison, Cluxton-Keller, & Gross, 2012; Levin & Parry, 2011). In contrast, majority published academic opinion in countries of Europe and Australasia as well as in India supporting the traditional/sceptical positions would have likely reduced the uptake of PBD diagnosis and psychopharmacological treatment in clinical practice. This was supported by a study of antipsychotic prescribing rates across 16 countries (Hálfdánarson et al., 2017), which found that all countries except Taiwan had less prescribing than the United States in the age range of 0 to 19 years, and US Medicaid data for socially disadvantaged children and youth showed particularly high rates. In fact, Medicaid data for 2001 to 2010 for the state of Kentucky showed that 2.4% of six-year-old children received a second-generation antipsychotic and from 2006, after Medicaid required prior authorisation with a diagnostic code, the most common diagnosis listed was BD (Lohr, Chowning, Stevenson, & Williams, 2015).

The influence of the traditional perspective on BD among academics in non-US countries may also be reflected in clinical practice with hospital discharge diagnosis rates for BD in the paediatric age range. Rates were found to be orders of magnitude lower in other nations compared to the United States (Clacey et al., 2015; Goetz et al., 2015; Kessing et al., 2014). This influence may also account for scepticism of PBD in surveys among child and adolescent psychiatrists in Germany (Meyer, Koßmann-Böhm, & Schlottke, 2004), Australia and New Zealand (Parry, Furber, & Allison, 2009), and the previously mentioned clinical vignette studies showing British child and adolescent psychiatrists having more conservative diagnostic practices compared to their US counterparts (Dubicka et al., 2008). This citation tree literature review supports this research and shows minimal spread of the PBD diagnosis, particularly in Canada, the UK, northern Europe, Asia, Australia and New Zealand.

The bibliometric analysis also reveals that a few authors from academic centres of child psychiatric research in Italy, Brazil, Spain, Turkey and South Korea have written articles supporting the PBD hypotheses. Most of these centres had co-authored articles with authors from US PBD research centres. Further research is required on the translation of the PBD diagnosis into clinical

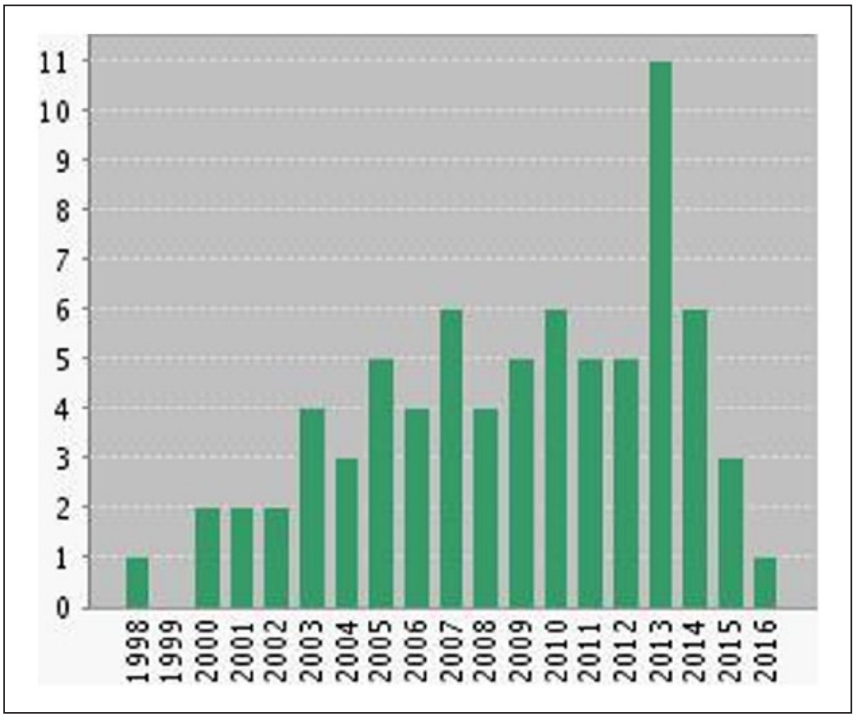

Figure 2. US plus international articles 1995–2016.

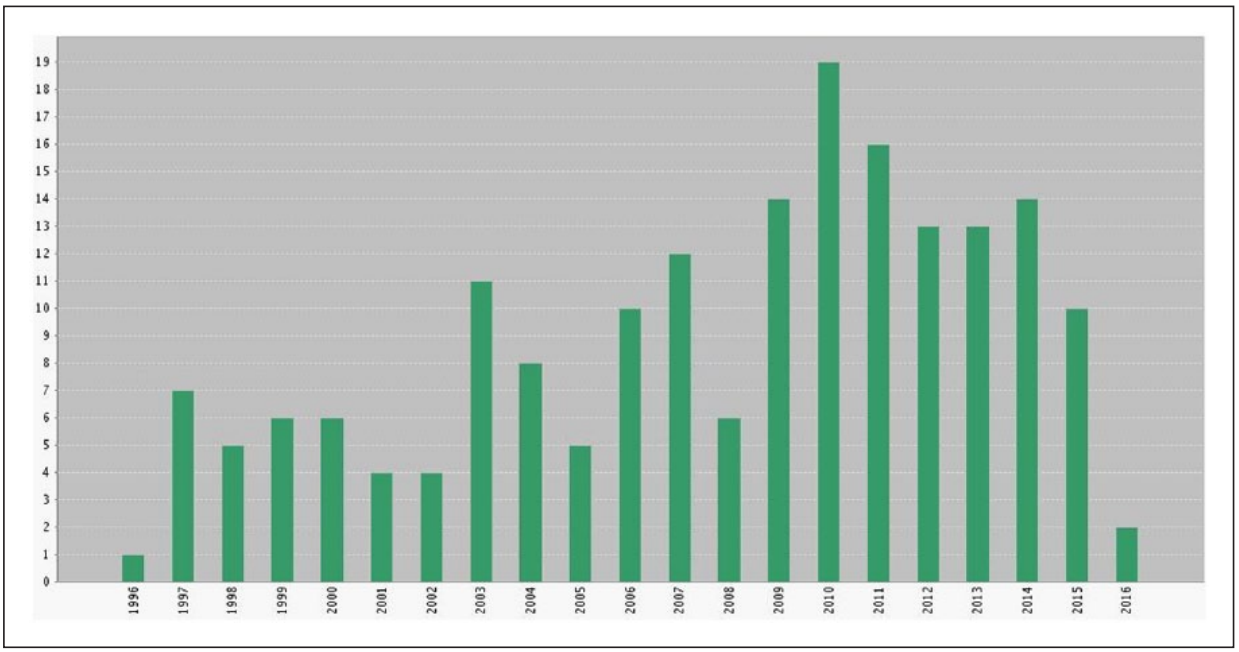

Figure 3. Non-US citing articles 1995–2016.

practice in Italy, Brazil, Spain, Turkey and South Korea, and the rates of off-label prescribing of second-generation antipsychotics and other medications.

Why are US academic institutions more likely to accept PBD?

These observations raise questions about what factors unique to the United States, and not present in most other countries, hastened the published academic acceptance of PBD.

First, pharmaceutical companies have developed a model of marketing-based medicine (Spielmans & Parry, 2010). As commercial entities, they are required to make profits for their shareholders, and this ensures that they are mainly oriented towards marketing, which is likely to influence choices in company-funded research and possibly presentation of the research outcomes. The four seminal articles proposing and promoting PBD presented US-based pharmaceutical companies with a marketing opportunity. The PBD diagnosis may well have allowed pharmaceutical companies to increase the sales of second-generation antipsychotics and other psychotropic medications as off-label prescriptions for children and adolescents. A US federal law passed in 2002, the 'Best Pharmaceuticals for Children Act', encouraged paediatric drug trials by granting six-month patent extensions to companies for drugs, if such paediatric drug trial data was submitted to the US Food and Drug Administration (FDA). Such patent extensions were worth billions of dollars for high-use drugs like second-generation antipsychotics. These commercial opportunities encouraged pharmaceutical companies to fund research and teaching on PBD by US academic psychiatrists. Lawsuits involving pharmaceutical companies subpoenaed internal industry documents that revealed companies were eager to collaborate with academic child psychiatrists in research that would expand the BD market (Levin & Parry, 2011; Moncrieff, 2014; Spielmans & Parry, 2010).

As these collaborative activities with academic leadership from some universities encouraged the remarkably rapid translation of PBD into clinical practice in the United States, unique aspects of the US health system were also crucial. PBD may have gained greater acceptance because the US health system often drives clinicians to engage in 'diagnostic upcoding' (Blader & Carlson, 2007; Harris, 2005; Roberts, 2017). Managed care has been anecdotally reported as providing more funding for a diagnosis like BD, than for diagnoses such as Oppositional-Defiant Disorder or parent–child relational problems. Roberts (2017) interviewed US clinicians and parents to uncover the factors leading to the 'genesis of a contested diagnosis' (p. 1.1) and quoted a child psychiatrist saying that to admit a child into a hospital 'it's easy to get the insurance to cover bipolar disorder' even acknowledging the ethical dilemmas of misdiagnosing to get an admission, saying: 'Fight the bureaucracy to do what's right, or just go along with it, and it puts me in a difficult position' (p. 1.9). Additional factors postulated for the rapid translation of PBD into clinical practice are as follows: a diagnosing culture that focuses on symptoms in brief 'med-check' appointments without time to explore the psychosocial context (Williams, 2008); over-reliance on parental questionnaires (Carlson, 1998); not engaging in comprehensive biopsychosocial formulations based on lengthy child and family sessions; a related lack of time or conceptual space to consider attachment and trauma issues; direct-to-consumer advertising by the pharmaceutical industry; the influence of lobby groups such as the Child and Adolescent Bipolar Foundation; the role of the US media in promoting PBD; and some best-selling books on PBD by US academics (Healy & Le Noury, 2007; McClellan, 2005; Parry & Levin, 2012).

These driving factors are less evident outside the United States, where academic opinion tends to support the traditional view of BD. It has been argued that the traditional view may be associated with PBD being underdiagnosed outside the United States. There might be delays in providing appropriate pharmacotherapy and psychoeducation for parents and their offspring with PBD. The principal factor contributing to such lower diagnostic rates would appear to be entrenched traditional perspectives on the nature and onset of BD in children and youth that prevails in most countries.

It is important to note that the PBD hypothesis was never universally accepted within the United States itself. As shown in Table 4, US authors co-wrote most (40 of 70; 57%) of the sceptical articles; however, they remained minority voices, making up only 11% of the total US output. Table 2 shows a substantial concentration of articles in several US academic institutions (in particular MGH/Harvard, University of Cincinnati, University of Pittsburgh and Case Western Reserve University), whereas other US academic institutions had fewer PBD-related articles or none. A drawback of

bibliometric methodology centred on published research is ascertaining the level of scepticism among those US clinicians who are unlikely to publish articles on something they do not diagnose. Although there have been no surveys of US child psychiatrists similar to the ones in Germany (Meyer et al., 2004), Australia and New Zealand (Parry et al., 2009) that have shown predominant scepticism of the PBD hypothesis, the trans-Atlantic comparison study (Dubicka et al., 2008) revealed diverging views among US child psychiatrists in diagnosing mania. This divergence is reflected in three of the vignettes. Sceptical-perspective articles by US-only authors (33) actually outnumbered articles with only non-US authors (30) in the citation tree analysis, there being seven articles with US and non-US co-authors. The research group at the US National Institute of Mental Health of Leibenluft and colleagues that developed the construct of Severe Mood Dysregulation, which was later accepted into *DSM-5* as Disruptive Mood Dysregulation Disorder, represented further scepticism of the PBD hypothesis, particularly with respect to 'broad-phenotype' PBD.

Comparison timelines show that overall the four seminal articles have fewer citing articles over time, suggesting their influence is decreasing. However, a progression of increased published academic interest from the United States to other countries was also evident, but this interest was better sustained where active collaboration between US PBD researchers and international researchers occurred. Previous bibliometric analysis has found that BD is more frequently diagnosed in the United States, Canada, Italy, Spain, Turkey and South Korea (Lariviere & Grant, 2016), and it is notable that PBD research is also mainly occurring in these countries.

'Liberal' versus 'conservative' perspectives on PBD

Even though not examined in this study, it should be mentioned that the PBD debate has occurred within an ongoing wider controversy of where to set the boundaries for BD in adults. Proponents of a more liberal 'bipolar spectrum disorder' construct, for example Akiskal and Pinto (1999) and Angst (2007), argue that cases of milder mood lability may be categorised as BD-NOS, or even Bipolar-III, Bipolar-IV, Bipolar-V disorders and may affect a much larger percentage of the population than classically considered. In contrast, those adhering to the more conservative, traditional perspective have critiqued this overdiagnosis as having a 'different phenomenology, family history, and course than classical bipolar disorders and [does] not respond in the same way to drugs' (Paris, 2009, p. 206), medicalising the 'everyday ups and downs' of life (Moncrieff, 2014, p. 593) and driven, at least in part, by pharmaceutical industry imperatives (Healy, 2006).

Carlson and Klein (2014) contrasted the 'liberal' perspective of the adherents to the PBD hypothesis with the 'conservative' classical perspective of how and when BD develops. They noted that the 'liberal' pro-PBD hypothesis leads to the diagnosis of many prepubertal cases and high rates of comorbid ADHD, whereas the traditional 'conservatively' diagnosed youth closely approximate BD-I in classically diagnosed adults and are diagnosed much less commonly. Findings regarding familial comorbidity from either of these perspectives reflected the underlying assumptions: Parents of PBD cohorts were more likely BD-NOS cases, whereas traditional BD-I/BD-II cohorts had parents with BD-I/BD-II phenomenology. Thus, methodology was based on how the boundaries of BD 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).

International diagnosis rates, particularly as reported since the Carlson and Klein (2014) article, further reflect this difference in perspective.

Perspectives regarding BD in the paediatric age range therefore remain highly divergent: We suggest that researchers and clinicians on both 'liberal' and 'conservative' sides of the debate engage in dialogue in the best interests of children and youth who exhibit mood lability and may either have BD or be at greater risk. There would appear to be a place for a major review article on BD in children and youth with academic opinion from both the 'liberal' pro-PBD and the 'conservative' sceptical/traditional BD-in-youth perspectives.

Limitations of this study

This citation tree analysis focused on published academic perspectives on a citation tree derived from four seminal articles. There are three particular limitations: (1) Whereas judgements on the perspectives of the articles relied on informed cognitive processes, bias could have been an influence. To somewhat compensate for this, supplementary information has been provided on how these judgements were made; (2) A more comprehensive collection of PBD-related articles, contrasting published academic perspectives in the United States with the rest of the world, might reveal a more nuanced account of the history of the academic debate over the last 20 years. (3) A further potential limitation is that the opinion of academics and clinicians who remained sceptical of the PBD hypothesis within the United States is likely to be under-represented in the published literature. The range of academic and clinical opinion on PBD within the United States, but also internationally, might be better ascertained by studies that used clinical vignettes similar to Dubicka et al. (2008) or surveys similar to those in Germany (Meyer et al., 2004), Australia and New Zealand (Parry et al., 2009). Another way of ascertaining the spread of the PBD hypothesis would be determining whether the content of child psychiatry training curriculums from various institutions support the 'liberal' PBD hypothesis or the 'conservative' traditional perspective of a late-adolescent to young-adulthood onset of BD.

Despite these limitations, the current study provides an overview of the international published perspectives on PBD, as both US-based and international researchers have cited the four seminal articles in their investigations and literature reviews of PBD. Thus, all the larger PBD research groups are likely to have been identified by the current study. In future studies, national differences in the academic perspectives on PBD could be compared to those on other child psychiatric diagnoses such as ADHD, Autism Spectrum Disorder and adolescent depression.

Conclusion

The four seminal articles investigated in this citation tree analysis proposed a paradigm shift, towards the diagnosing of BD in childhood and early adolescence, which had major implications for clinical practice, especially in the United States. The evidence suggests that the four articles have attracted support from a number of academic centres in the United States over the last two decades but encountered a limited and mixed response from academics in the rest of the world. There are indications that the PBD hypothesis remained controversial within the United States but received support from prominent US psychiatric journals. Most published academics outside the United States have taken a traditional or sceptical perspective on PBD with the exception of pro-PBD perspectives in academic child psychiatric centres in Italy, Brazil, Spain, Turkey and South Korea.

These well-established disparities in published academic opinion are problematic as they prevent an international consensus on the management of childhood mood lability that may or may not signify emerging BD. Published academic advice has been shown to influence treatment decisions made by clinicians such as raising the prescription rates of second-generation antipsychotics (Domino & Swartz, 2008). Hence, currently a child's geographical location partly determines his

or her treatment. Further effort is required on the development of an international consensus among academic and clinical child psychologists, psychiatrists and allied professionals on the management of childhood mood lability.

Acknowledgements

The authors are grateful to Brenda Jericho for proof reading the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Supplemental material

Supplemental material for this article is available online.

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Does the ISBD Task Force Report overestimate the prevalence of Pediatric Bipolar Disorder?

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Introduction:

Proposed community prevalence of PBD at high rate similar to adult rate of BD

The recent International Society for Bipolar (ISBD) Task Force Report estimated that the international community prevalence for Pediatric Bipolar Disorder (PBD) is 2.06%, based on a meta-analysis of 18 epidemiological studies (Goldstein et al., 2017).

This high prevalence estimate indicates that millions of children and adolescents around the world may have undiagnosed bipolar disorder (BD).

If the ISBD Task Force prevalence estimate is too high, however, it may encourage the over-diagnosis of BD in children who could receive unnecessary treatment that causes iatrogenic harm with prescription of second-generation-antipsychotics, sometimes badged as 'mood stabilizers', that can cause sudden death mostly from cardiac arrest (Ray et al., 2018) as well as potentially cerebral atrophy (Bastiampillai et al., 2018) as well as metabolic and neurological adverse effects.

In making its estimate, the ISBD Task Force Report drew upon a highly cited meta-analysis of 12 epidemiological studies (Van Meter et al., 2011) that claimed an international community prevalence of 'PBD' of 1.8%. However, our previous review of the individual studies used in Van Meter et al. meta-analysis found that the prevalence of PBD was lower than claimed, and that BD was rarely detected before puberty (Parry et al., 2018; Table 1). Our re-analysis was followed by an international nine-article debate about PBD (Carlson & Dubicka, 2019; Van Meter et al., 2019; Parry et al., 2019; Goldstein et al., 2019; Pan et al., 2019; Hazell, 2019; Duffy, 2019; Hillegers, 2019; Stringaris, 2019) in the journal *Child and Adolescent Mental Health (CAMH).*

The ISBD Task Force updated Van Meter et al. (2011)'s meta-analysis by using "an identical search strategy [to] identify six new studies" (p. 525). These studies were two from Brazil (Anselmi et al., 2009; Pan et al., 2014), and single studies from the USA (Roberts et al., 2007), Germany (Tijssen et al., 2010), Canada (Kozloff et al., 2010) and Sweden (Päären et al., 2014).

By combining all 18 studies the ISBD Task Force reported a total study population of: "31,443 youth aged 7-21 years, 576 of whom met criteria for bipolar spectrum disorders" and by applying meta-analysis they found an "updated weighted average prevalence of bipolar spectrum disorders [of] **2.06%** (95% CI 1.44%-2/95%)" (p. 526).

In the current study, we extend our previous review of the individual epidemiological studies to include the six additional studies included in the ISBD Task Force Report on PBD to examine the evidence for early onset BD.

Methods:

The original 12 epidemiological surveys were examined with a qualitative narrative analysis focussing on the methodologies of the studies (Parry et al., 2018). The six newer studies were treated in the same manner. New prevalence rates were established by correcting for each of the factors listed below.

An important confounder noted by Goldstein et al. (2017) was the definition of BD: whether it includes BD-NOS/all bipolar spectrum diagnoses, or just BD-I and BD-II. The use of the term 'PBD' generally includes all BD-NOS and bipolar spectrum diagnostic categories

Results:

The 18 surveys were unsuitable for meta-analysis because the methodologies varied widely in instrumentation, ages of subjects, concordance between informants, prevalence period, and diagnostic criteria (Deeks, Higgins and Altman, 2011).

There was wide variation in the reported prevalence rates, due to the differing definitions of PBD, heterogeneity of study methods, and combining parent and youth reports, even if discrepant. PBD prevalence rates were zero or close to zero in surveys of prepubertal children.

The meta-analysis by Van Meter and colleagues (2011) generally took the higher prevalence rates from the original surveys. For example, they utilised the rate of bipolar spectrum disorder of 2.8% in the Dutch survey (Verhulst et al., 1997) by adding parent and youth reports. However, if prevalence were to be based on parent and youth concordance, then the rate was 0%.

The methodologies for the first 12 surveys, and the differing prevalence rates that can be derived depending upon how they are used, are illustrated in Table 1. A narrative commentary on each of the 12 studies is provided in Parry et al. (2018).

Table 1: The 12 epidemiological studies meta-analysed by Van Meter et al. (2011)

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 years	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 years	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 years	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 years	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 years	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 years	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 years	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 years	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 years	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 years	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 years	Adolescent only informant	6.3% (K-SADS)	0.5% (K-SADS) 1.0% (CIDI)	6.2% (K-SADS) 6.6% (CIDI)

There was little evidence that mania/hypomania was detected amongst pre-pubertal children in international community samples. Päären et al. (2014) reported one adolescent with a manic episode and in 15-year follow-up found that 'hypomania spectrum disorder' in adolescence rarely progressed to adult BD – Adult mania was reported by only 2 among 64 follow-up participants (3%), and hypomania was reported by an additional 4 participants (6%) (Päären et al., 2013); Tijssen et al. (2010) only report on adolescents; Roberts et al. (2017) found 0.22% of adolescents had mania/hypomania and impairment; Kozloff et al. (2010) only report on youth; Anselmi et al. (2009) found a zero rate of BD amongst pre-pubertal children; and Pan et al. (2014) found a 0.2% rate of BD-I/BD-II in childhood, but raised significant questions around the overlap with externalising disorders and lack of impairment in the BD-NOS group.

The further six surveys covered by the ISBD Task Force Report are illustrated in Table 2.

Table 2: The six extra epidemiological studies reported on by the ISBD Task Force

Source Subjects	Location Year completed Criteria	Instrument Prevalence period Age	Critique	BD-I %	Total 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	1/2,300 = 0.04% fulfilled criteria for a manic episode	62/2,300 = 2.7%
Tijssen et al, 2010 N = 1,395 or 705	Germany 1997-1999 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	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.	0.39% (with/out impairment) 0.31% (DISC impairment) 0.22% (CGAS impairment)	1.2% 0.31% 0.31%
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".	Not defined	All ages 15-24 years: 3.0% 15-18 years: 2.1% 19-24 years: 3.8%
Anselmi et al, 2009 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]	Child plus mother informants combined with psychiatrist adjudication where discrepant	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% (BD-I/BD-II) 0.2%* (* weighted prevalence – pers. comm. Pan-Parry, 2019)	1.8% 1.4%* (* weighted prevalence – pers. comm. Pan-Parry, 2019)

Conclusions:

Our re-examination of the epidemiological surveys found that BD was rarely detected before mid-adolescence, which is consistent with the findings of most high-risk offspring studies where bipolar disorder usually begins after mid-adolescence (Duffy et al., 2017).

This finding is significant as it suggests BD is rare in community samples before adolescence, and casts doubt on the notion that there are huge numbers of pre-pubertal children around the world with undiagnosed BD.

Stringaris (2019) notes that whilst under-diagnosis of early onset BD may be a problem outside the USA, over-diagnosis is probably "an even worse problem" within parts of the USA. He cites Lohr et al. (2015) for finding that BD "accounted for the majority of [antipsychotic] prescriptions among the younger than 7-year-olds" with "a staggering 2.4% of 6-year-olds" (p. 106) on mostly long-term antipsychotic medication in the state of Kentucky. Lohr et al. (2015) reported that the Medicaid data indicated a three-fold difference between western and eastern Kentucky in prescribing rates, indicating geographical variation in applying the PBD diagnosis within the USA as well as internationally.

In conclusion, our narrative re-examination suggests that bipolar disorder is rare before later adolescence, which is consistent with lower diagnostic rates in Europe and Australasian clinical cohorts (Clacey et al., 2015).

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