Appendix A6

Paediatric Bipolar Disorder: the View from Australia & New Zealand

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Background

Paediatric bipolar disorder (PBD) refers to phenotypes of bipolar disorder postulated to represent the illness in children and adolescents in a manner different to classical mainly adult descriptions of the disorder. Diagnostic criteria were developed in the early to mid 1990s in the USA [1]. In the USA rates of diagnosis of bipolar disorder in children and teens increased 4,400% from 1994/5 to 2002/3 [2].

However other countries have been slow to adopt similar diagnostic patterns. Inpatient units in the UK and Denmark have rarely diagnosed mania or bipolar disorder. A 22 year retrospective study at the Maudsley [3], defined only 38 cases of either bipolar disorder or psychotic depression, with mean age of 14.2 years (range 11 to 18). None of 2,500 children 10 years or younger referred to the Royal Manchester Children's Hospital Dept. of Psychiatry had a diagnosis of mania or bipolar disorder [4]. In Denmark, only 39 cases (1.2%) of psychiatrically hospitalised children aged 15 and under between 1970 and 1986 were diagnosed with bipolar disorder [5].

A survey of 261 (61% response) German child and adolescent psychiatrists revealed only 8% claimed to have diagnosed a pre-pubertal child with bipolar disorder [6].

The British National Institute for Health and Clinical Excellence (NICE) guidelines on bipolar disorder, 2006, adopt a conservative approach and advise PBD diagnoses should be reserved only for research purposes [7].

The international differences persist in research on retrospective recall of illness onset amongst adults with bipolar disorder. 22% of a US cohort claimed onset of depressive or manic/hypomanic episodes prior to age 13 whilst only 2% of German and Dutch adult sufferers did so [8].

In Australia and New Zealand (ANZ) there was little mention of PBD in academic or clinical circles until the 2004 meeting of the Faculty of Child & Adolescent Psychiatry of the Royal Australian and New Zealand College of Psychiatrists (FCAP of RANZCP) when Birmaher from the USA presented on the topic [9]. A symposium at the May 2007 RANZCP Congress [10] gave further information. A 2006 pilot survey of the FCAP of RANZCP with 26% response rate [11] did however show 21% of respondents had shifted their views towards seeing more bipolar disorder cases in recent years, none saw less, whilst 79% hadn't shifted their views.

Method

A 16-item plus general comments survey of the 328 members of the FCAP of RANZCP was conducted in late 2007 via mail-out and online questionnaires preserving anonymity and with Flinders Clinical Research Ethics Committee approval.

The aim was to discover opinions of child & adolescent psychiatrists within ANZ on PBD diagnosing patterns both within ANZ and in the USA. 199 (60%) responded, mean years of experience in CAP was 15.09 (SD 9.57).

Results

Results of the 16 item questionnaire have been published in the journal *Child and Adolescent Mental Health* Vol 14, 3, 2009, pp 140-147 as "The paediatric bipolar hypothesis: the view from Australia and New Zealand."

Some key findings were that the majority (83%) viewed pre-pubertal bipolar disorder as "very rare", "rare" or "undiagnosable" and 53% had never seen a case. In contrast, 57% saw adolescent bipolar disorder as "uncommon" and only 3% had never seen a case.

To the question "estimate the number of pre-pubertal/adolescent cases of bipolar disorder you have diagnosed in the last 12 months?", tables 1 & 2 show the difference between pre-pubertal and adolescent groups.

Table 1.

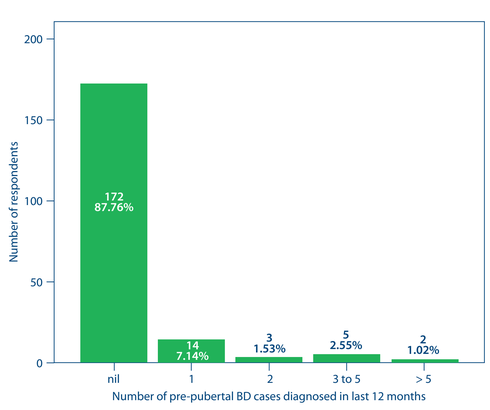
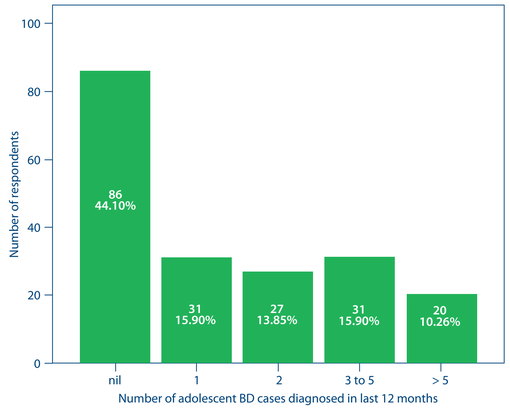
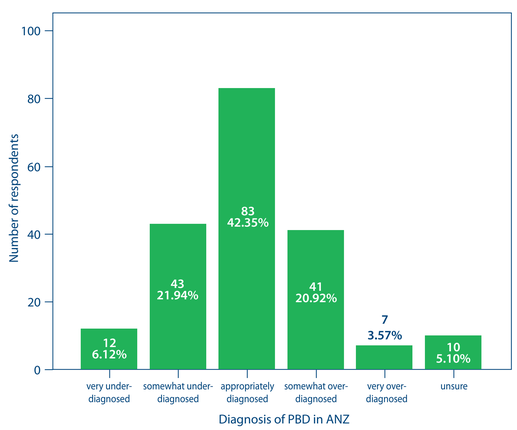


Table 2.



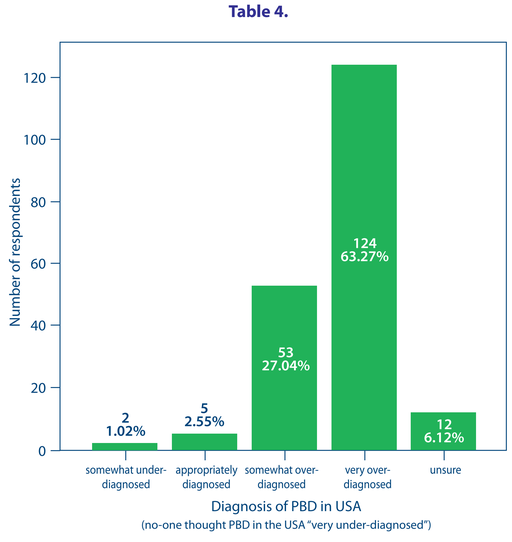
There was a divergence of views (table 3) as to whether PBD was appropriately diagnosed, underdiagnosed or overdiagnosed in ANZ.

Table 3.



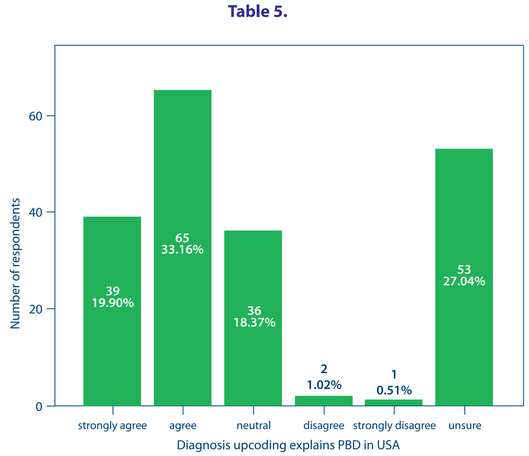
In contrast there was a clear consensus (table 4) that PBD was overdiagnosed in the USA.

Table 4.



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 managed care health system) was a causative factor, a majority (53%) felt it was and only 1.5% disagreed (table 5).

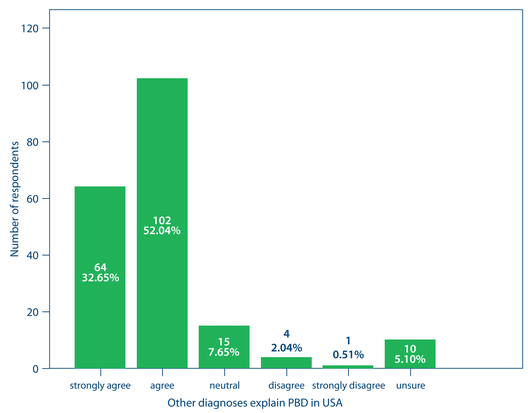
Table 5.



8.7% of respondents agreed and 4.1% strongly agreed with the proposition "other diagnoses (e.g., ADHD, Anxiety, Adjustment disorders, PTSD, parent-child problem, peer relationship problem) in ANZ should in fact be diagnosed as PBD." whilst 23.6% disagreed, 54.9% strongly disagreed and 8.8% were neutral/unsure.

Conversely, to the question whether the same "other diagnoses..." "probably explain many of the cases of PBD in the USA" the majority agreed (table 6).

Table 6.



There was considerable variation and uncertainty and lack of clear trend in responses to the other questions as to whether manic switching or the activation syndrome from SSRIs could account for many cases of PBD in the USA.

General Comments:

75 respondents gave comments. These were not included in the paper in *Child and Adolescent Mental Health*, however they add depth to the responses and several themes emerged, and examples were published in the FCAP of RANZCP e-Bulletin Nov 2008; examples included:

There were 11 comments **generally favourable to increased diagnosis of PBD.** These tended to include caveats about overmedicating and noted issues of difficulty in diagnosis and comorbidity, e.g.:

"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."

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

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

"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."

4 comments that PBD followed **overdiagnosis of BD in adults**, e.g.:

"...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'."

10 comments about **shift from biopsychosocial to biomedical model**, e.g.:

"...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."

7 comments referring to the **American health system**, 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."

9 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."

2 comments that **normal 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."

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

"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."

Conclusions

Although a minority of ANZ child & adolescent psychiatrists appear to have shifted their views in recent years, the majority view was consistent with classical descriptions of bipolar disorder and rather sceptical of PBD phenotypes as used particularly in the USA.

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Appendix A11

What Do Internal Industry Documents Suggest About Sponsored Drug Trials?

"The larger issue is how do we face the outside world when they begin to criticize us for suppressing data..."

AstraZeneca public relations manager in internal email 6 Dec 1999.

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GLEN SPIELMANS, PhD, Metropolitan State University, Minnesota, USA.

Disclosures: PP is a member of *www.healthyskepticism.org*
GS has <$10,000 in Vanguard Health Care that invests in pharmaceutical industry.

Background

There is increasing concern over bias in industry sponsored drug trials. The odds ratio of a sponsored drug trial producing a favourable outcome for the sponsor's drug has been calculated as 4.05 (95% CI 2.98 - 5.51) in a meta-analysis of 18 review articles (Lexchin et al, BMJ, 2003).

This problem has an extensive literature e.g.:

- "Industry sponsored research: a broken system." (Angell, JAMA, 2008); *n.b. Marcia Angell is a former chief editor of the NEJM.*
- "How pharmaceutical industry sponsorship affects trial outcomes: causal structures and responses." (Sismondo, *Soc Sci Med, 2008*);
- "Bias, spin, and misreporting: time for full access to trial protocols and results." (Chan, *PLoS Med*, 2008);
- "Medical journals are an extension of the marketing arm of pharmaceutical companies." (Smith, *PLoS Med*, 2005). *n.b. Richard Smith was 25 years editor at the BMJ, last 13 chief editor.*

In recent years internal pharmaceutical company documents have come to light as subpoenaed evidence in litigation against the pharmaceutical industry. Some of these concerned GSK (formerly SKB) study 329 comparing paroxetine, imipramine and placebo in adolescent depression (published as Keller et al, *J Am Acad Child Adolesc Psychiatry*, 2001). These documents spurred regulatory efforts to examine unpublished as well as published data on use of SSRIs in adolescence and ultimately led to the current product label warnings. A database of study 329 documents is available at www.healthyskepticism.org/documents/PaxilStudy329.php

One internal SKB/GSK document quoted in an editorial in the *Canadian Medical Association Journal*, ("Drug company experts advised staff to withhold data about SSRI use in children." Kandro, *CMAJ* 2004)) is "Seroxat/Paxil Adolescent Depression: Position piece on the phase III clinical studies" by the Central Medical Affairs team (CMAT) of SKB/GSK and excerpts are in Fig 1 and Fig 2:

Fig 1. SKB/GSK CMAT document re study 329 excerpt.

TARGET

To effectively manage the dissemination of these data in order to minimise any potential negative commercial impact.

PROPOSALS

- Based on the current data from Studies 377 and 329, and following consultation with SB country regulatory and marketing groups, no regulatory submissions will be made to obtain either efficacy or safety statements relating to adolescent depression at this time. However data (especially safety data) from these studies may be included in any future regulatory submissions, provided that we are able to go on and generate robust, approvable efficacy data. The rationale for not attempting to obtain a safety statement at this time is as follows;

  i) regulatory agencies would not approve a statement indicating that there are no safety issues in adolescents, as this could be seen as promoting off-label use

  ii) it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.

- Positive data from Study 329 will be published in abstract form at the ECNP (Paris, November 1998) and a full manuscript of the 329 data will be progressed.

An internal memo from Pfizer (July 27, 2000) suggests - "the purpose of data is to support, directly or indirectly, marketing of our product."

Fig. 2. Document regarding marketing of sertraline (Pfizer)

Data "Ownership" and Transfer

- Pfizer-sponsored studies belong to Pfizer, not to any individual
- Purpose of data is to support, directly or indirectly, marketing of our product
  - Through use in label enhancements, sNDA filings
  - Through publications for field force use
  - Through publications that can be utilized to support off-label data dissemination
- Therefore commercial marketing/medical need to be involved in all data dissemination efforts

CONFIDENTIAL

Szyndrek/291460

Recent Documents from Manufacturers of Seroquel and Zyprexa

Recent documents subpoenaed and released from class action and attorney general prosecuted trials in USA jurisdictions involve AstraZeneca (Seroquel) and Eli-Lilly (Zyprexa). The documents are hosted on www.furiousseasons.com and www.healthyskepticism.org/documents/Antipsychotics.php

Much of the material in these documents concerns marketing issues. Some of these marketing issues are examined in "The promotion of olanzapine in primary care: an examination of internal industry documents." (Spielmans, *Soc Sci Med*, 2009)

In May 2000, a presentation (Schulz) at the American Psychiatric Association indicated that AZ's atypical antipsychotic quetiapine possessed greater efficacy in reducing symptoms of schizophrenia than haloperidol. The presentation was based on a meta-analysis of four studies comparing the two compounds. A press release accompanying the May 2000 conference presentation stated the presenter hoped *"that our findings help physicians understand the dramatic benefits of newer medications like Seroquel."* (PR Newswire, New York, May 16, 2000).

However, an internal document titled "BPRS meta-analysis" with "date printed 3/9/2000" from AZ's "Commercial Product Team" (Omnibus MSJ exhibit 2) contains an internal AZ meta-analysis of 10 Seroquel versus placebo and comparator drugs which is summarised in a table (excerpt in fig. 3) and referred to in an email (fig. 4):

Fig 3. AZ internal meta-analysis of Seroquel v 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	✗	✗	✗	✗	-	✗	✗

Fig 4. AZ email re meta-analysis of Seroquel v 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.

One study, not included in the above meta-analysis, comparing haloperidol with quetiapine was Study 15, referred to (fig. 5) as "this cursed study". The trial report showed significantly fewer patients experienced a psychotic relapse on haloperidol relative to quetiapine; symptom measures also significantly favoured haloperidol. These efficacy results were not published. However quetiapine's benefit over haloperidol on some cognitive measures were published (Velligan et al. *Schizophrenia Res* 2002.). Two years later a further email discusses study 15 and other "buried" studies (fig. 6).

Fig. 5 email re "cursed" study 15

INTERNAL MEMORANDUM

Date: 12-Feb-1997 03:40am EDT
Tel No: 01625 517679
To: See Below
From: Richard Lawrence
Subject: RE: US/Canada Investigator meeting and Study 15

I am not 100% comfortable with this data being made publically available at the present time....however I understand that we have little choice....Lisa has done a great 'smoke -and-mirrors' job!

Adopting the approach Don has outlined should minimise (and dare I venture to suggest) could put a positive spin (in terms of safety) on this cursed study.

Athena, with Mark Sahl having left I am not certain who is replacing him. Whoever it is..... ought they speed a reserve press release through?

Fig. 6 email re use of study 15 as "cherry picking" and mention of "buried" studies

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.

A particularly interesting document is an email from AZ's *Global Brand Manager-Seroquel to the Seroquel Global Brand Team* dated "8/7/2003" that describes a survey of AZ employees who had previously worked for other pharmaceutical companies or KOL's (key opinion leaders) on practices for managing *Investigator Initiated Trials* (IITs) i.e. research where lead author is not employed by a pharmaceutical company. Excerpts are presented here:

"A series of interviews were carried out with internal AZ staff who were known to have worked for competitor companies before as well as a number of KOL investigators...
The objective...to find out...where and why our competitors invest in IITs.
Key messages emerging from the report:

- *Lilly run a large and highly effective IIT program*
  ...offer significant financial support but want control of the data in return
  ...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 favorable results but they are well rewarded...
  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..."

Eli Lilly drafted a document regarding plans to write a manuscript featuring intramuscular olanzapine, set to coincide with its market launch. The "author" was to be a key opinion leader who may or may not actually draft the manuscript.

Fig. 7 excerpt from undated document re writing a journal article to help launch IM olanzapine

Authoring of the feature article

- Utilise a local KOL to author the feature, either by drafting the full feature for KOL review or by giving the outline to a KOL to develop the feature.
- The KOL has full editorial control over the feature; if they wish to make changes, this should be encouraged and accomodated.
- The KOL could be:
  - An investigator in an olanzapine intramuscular trial.
  - Lilly-friendly key opinion leader, who has previously been involved in other areas of olanzapine.
  - A participant of a Lilly advisory board.
- KOLs can be paid honorarium for their time/input in reviewing/authoring of the article. It should be made clear that this payment is for their time and not to sway the content of the article. If using a member of a relevant advisory board, KOL authoring could be covered by a retainer given for participation in advising the board. This is the best option to use, if possible.

Conclusions

Documents such as these are not confined to psychotropics e.g. with regard to Merck's analgesic "Vioxx", Psaty & Kronmal, *JAMA*, 2008: "Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: A case study based on documents from rofecoxib litigation."

As Chan notes "trust (in randomized trials in the medical literature) has been eroded due to several high-profile cases of alleged data suppression, misrepresentation and manipulation."

Smith says it took him "almost a quarter of a century editing for the *BMJ* to wake up to what was happening" - how drug trial data can be manipulated. He summarises the methods as he sees them (fig. 8).

Fig. 8. from Smith, R. PLoS Medicine 2005 (reproduced with permission)

Examples of Methods for Pharmaceutical Companies to Get the Results They Want from Clinical Trials

- Conduct a trial of your drug against a treatment known to be inferior.
- Trial your drugs against too low a dose of a competitor drug.
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
- Conduct trials that are too small to show differences from competitor drugs.
- Use multiple endpoints in the trial and select for publication those that give favourable results.
- Do multicentre trials and select for publication results from centres that are favourable.
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress - for example, reduction in relative rather than absolute risk.

In an echo of the subprime mortgages sprinkled through financial derivatives that sparked the Global Financial Crisis, the medical literature now suffers a crisis of trust as editors, peer-reviewers and readers cannot be sure what to believe. Smith, Chan and many others propose solutions such as full access to raw data, though these are beyond the scope of this presentation.

Limitations

The industry argues in court that subpoenaed documents are taken out of context. This may be so and 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.