International Journal of Risk & Safety in Medicine 19 (2007) 209–221
IOS Press

Pediatric bipolar disorder: An object of study in the creation of an illness

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Abstract. In the past decade bipolar disorder in children has been diagnosed with rapidly increasing frequency in North America, despite a century of psychiatric consensus that manic-depressive illness rarely had its onset before adolescence. This emergence has happened against a background of vigorous pharmaceutical company marketing of bipolar disorder in adults. In the absence of a license demonstrating efficacy for their compound for bipolar disorder in children, however, companies cannot actively market pediatric bipolar disorder. This paper explores some mechanisms that play a part in spreading the recognition of a disorder in populations for which pharmaceutical companies do not have a license. These include the role of academic experts, parent pressure groups, measurement technologies and the availability of possible remedies even if not licensed.

Keywords: Bipolar disorder, mood-stabilizers, mood-watching, disease mongering, off-label prescribing

1. Introduction

The diagnosis of bipolar disorder is rapidly increasing in frequency in North America. It seems commonly assumed that pharmaceutical companies must have engineered this.[1] However, no company has a license for treating bipolar disorder in children and hence no company can advertise their drug for use in children in either academic or lay outlets. As such this disease cannot be mongered as readily as social anxiety disorder, panic disorder or other such entities.

This paper seeks to explore the capacities of companies to create a culture that legitimizes practices that would otherwise appear extra-ordinary. The article aims at offering a historically accurate narrative that shares many background themes in common with developments in other medical disorders, but which has in its foreground a comparatively small number of actors whose roles may merit further research. The narrative illustrates how company strategies in one domain can resonate in another, in this case the pediatric domain. To bring this point out, we first describe the marketing of adult bipolar disorder.

2. The marketing of adult bipolar disorder

Just as other corporations do, pharmaceutical companies attempt to establish what marketing departments refer to as the unmet needs of their market [2]. One mechanism is to use focus groups; in the case

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[1] It seems to the authors that this assumption is common and it seems unlikely that this increase in diagnosis would be happening in the absence of possible treatments clinicians could give.

of psychotropic drugs, focus groups consist of academic psychiatrists, also termed opinion leaders. In this process, academics have three roles. As repositories of psychiatric knowledge they help companies understand what the average clinician might perceive as a development. As opinion leaders they help deliver the company message to non-academic clinicians. As academics, they lend their names to the authorship lines of journal articles and presentations at professional meetings reporting the results of company studies or discussing clinical topics of strategic interest to marketing departments [20].

From work like this with opinion leaders in the early 1990s, a series of unmet mental health needs clustering around the concept of bipolar disorder were identified. The field was prepared to believe that bipolar disorder could affect up to 5% of the population; that it was an unacknowledged and under-researched disorder; that antidepressants might not be good for this disorder; that treatment might be better focused on the use of a "mood stabilizer"; and that everybody stood to gain by encouraging patients to self monitor.

Early market research was linked to the introduction of Depakote. In the form of sodium valproate, this anticonvulsant had been available and shown to be helpful in manic-depressive illness from the mid-1960s. Abbott Laboratories reformulated it as semi-sodium valproate,[2] which it was claimed formed a more stable solution than sodium valproate. This trivial distinction was sufficient to enable the company to gain a patent on the new compound, which as Depakote was introduced in 1995 for the treatment of mania. Depakote was approved by the Food and Drugs Administration on the basis of trials that showed this very sedative agent could produce beneficial effects in acute manic states [37]. Any sedative agent can produce clinical trial benefits in acute manic states but no company had chosen to do this up till then, as manic states were comparatively rare and were adequately controlled by available treatments.

Depakote was advertised as a "mood stabilizer". Had it been advertised as prophylactic for manic-depressive disorder, FDA would have had to rule the advertisement illegal, as a prophylactic effect for valproate had not been demonstrated to the standards required for licensing. The term mood stabilizer in contrast was a term that had no precise clinical or neuroscientific meaning [15]. As such it was not open to legal sanction. It was a new brand.[3]

Depakote was referred to exclusively as a mood stabilizer rather than an anticonvulsant, even though there still have not been any studies that prove it to be prophylactic for manic-depressive illness. This branding played a major role in leading to increased sales of the compound compared for instance to sodium valproate, which had better evidence for efficacy but was never referred to as a mood stabilizer. Although the term still has no precise clinical or neuroscientific meaning, mood stabilizers have become the rage, with a range of other agents passing themselves off as mood stabilizers. Before 1995 there were almost no articles in the medical literature on mood-stabilizers but now there are over a hundred a year [21]. Both clinicians and patients seem happy to endorse this rebranding of sedatives despite a continuing lack of evidence that these drugs will achieve their stated aim.

But in addition to branding a new class of psychotropic drugs, the 1990s saw the rebranding of an old illness. Manic-depressive illness became bipolar disorder. While the term bipolar disorder had been introduced in DSM-III in 1980, as late as 1990 the leading book on this disease was called Manic-Depressive Disease [16]. It is rare to hear the term manic-depressive illness now. This combination of a brand new disease and brand new drug class is historically unprecedented within psychiatry.

[2]United States Patent 4,988,731. Date of Patent Jan. 29th 1991; United States Patent 5,212,326. Date of Patent May 18th 1993.

[3]While the term mood-stabilizer is not a trade-marked term, this use of the word brand here is deliberate. While the drugs are products, the identification of these previously existing products under one advertising rubric such as mood-stabilizer or SSRI appears to conform to the notion of a brand.

Lilly, Janssen and Astra-Zeneca, the makers of the antipsychotic drugs, olanzapine (Zyprexa), risperidone (Risperdal) and quetiapine (Seroquel), respectively sought indications in this area and the steps they have taken to market their compounds as mood stabilizers illustrate how companies go about making markets. We will outline six such steps.

First, each company has produced patient literature and website material aimed at telling people more about bipolar disorder, often without mentioning medication; this is a feature of what has been termed disease mongering [32]. In the case of Zyprexa, patient leaflets and booklets – routed in Britain through a patient group, the Manic-Depressive Fellowship – aim at telling patients what they need to do to stay well. Among the claims are "that bipolar disorder is a life long illness needing life long treatment; that symptoms come and go but the illness stays; that people feel better because the medication is working; that almost everyone who stops taking the medication will get ill again and that the more episodes you have the more difficult they are to treat".[4]

A similar message is found in a self-help guide for people with bipolar disorder sponsored by Janssen Pharmaceuticals which under a heading 'the right medicine at the right time' states: "Medicines are crucially important in the treatment of bipolar disorders. Studies over the past 20 years have shown without a shadow of doubt that people who have received the appropriate drugs are better off in the long term than those who receive no medicine" [8].

If studies had shown this, there would be a number of drugs licensed for the prophylaxis of bipolar disorder when in fact until recently lithium was the only drug that had demonstrable evidence for prophylactic efficacy but even this had not received a license from the FDA. More to the point all studies of life expectancy on antipsychotics show a doubling of mortality rates on treatment compared to the non-treated state and this doubling increases again for every extra antipsychotic drug that the patient takes [25]. Patients taking these drugs show a reduction of life expectancy of up to 20 years compared to population norms [6].

Furthermore, to date when all placebo-controlled studies of Depakote, Zyprexa and Risperdal in the prophylaxis of bipolar disorder are combined they show a doubling of the risk of suicidal acts on active treatment compared to placebo [21,38]. In addition, valproate and other anticonvulsants are among the most teratogenic in medicine [10].

These claims about the benefits of treatment therefore appear misleading. No company could make such public statements without the regulators intervening. But by using patient groups or academics, companies can palm off the legal liability for such claims [20].

A second aspect of the marketing of the drugs uses celebrities such as writers, poets, playwrights, artists and composers who have supposedly been bipolar. Lists circulate featuring most of the major artists of the 19th and 20th Century intimating they have been bipolar, when in fact very few if any had a diagnosis of manic-depressive illness.

A third aspect of the marketing has involved the use of mood diaries. These break up the day into hourly segments and ask people to rate their moods on a scale that might go from $+5$ to -5. For example, on the Lilly sponsored mood diary,[5] one would rate a $+2$ if one was very productive, doing things to excess such as phone calls, writing, having tea, smoking, being charming and talkative. For a score of $+1$ your self-esteem would be good, you are optimistic, sociable and articulate, make good decisions and get work done. Minus 1 involves slight withdrawal from social situations, less concentration than

[4]Staying Well... with bipolar disorder. Relapse Prevention Booklet. Produced in Association with the Manic-Depressive Fellowship of Great Britain, Sponsored by Eli Lilly and Company (2004), page 17.

[5]Mood diary produced in consultation with the Manic-Depressive Fellowship of Great Britain, Sponsored by Eli Lilly & Company (2004). Other companies have similarly sponsored mood diaries.

usual and perhaps slight agitation. Minus 2 involves feelings of panic and anxiety with poor concentration and memory and some comfort in routine activities. Most normal people during the course of the week will probably cycle between at least +2 and −2, which is almost precisely the point behind this mood-watching. Most normal people will show a variation in their moods that might be construed as an incipient bipolar disorder.

On IsItReallyDepression.com,[6] Astra-Zeneca, the makers of Seroquel (quetiapine), provide a mood questionnaire which asks whether there has been a period when you were more irritable than usual, more self-confident than usual, got less sleep than usual and found you didn't really miss it, were more talkative than usual, had thoughts race through your mind, had more energy than usual, were more active than usual, were more social or outgoing than usual, or had more libido than usual.

These are all functions that show some variation in everyone. Answering Yes to 7 of these, leads to two further questions one of which is whether you have ever had more than one of these at any one time and the second of which is whether you have ended up in any trouble as a result of this. If you answer yes to these two questions you may meet criteria for bipolar disorder and are advised to seek a review by a mental health professional. Whether or not you meet criteria, if concerned, it is suggested you might want to seek a mental health review.

This measurement induced mood watching has an historical parallel in the behavior of weight watching that came with the introduction of weighing scales [19]. This new behavior coincided with the emergence of eating disorders in the 1870s. There was subsequently an increase in frequency in eating disorders in the 1920s that paralleled a much wider availability of weighing scales and the emergence of norms for weight that had a rather immediate impact on our ideas of what is beautiful and healthy. In the 1960s there was a further increase in the frequency of eating disorders and again this paralleled the development of smaller bathroom scales and their migration into the home. While there are undoubtedly other social factors involved in eating disorders, it is a moot point as to whether eating disorders could have become epidemic without the development of this measurement technology.

There is an informational reductionism with mood diaries that is perhaps even more potent that the biological reductionism to which critics of psychiatry often point. Measuring is not inherently a problem and figures may provide potent reinforcement to behaviors, but the abstraction that is measurement can lead to an oversight for context and other dimensions of an individual's functioning or situation that are not open to measurement or that are simply not being measured. If these oversights involve significant domains of personal functioning, we are arguably being pseudoscientific rather than modestly scientific in measuring what we can.

A fourth aspect of the current marketing of all medical disorders involves the marketing of risk. This is true for the marketing of depression and bipolar disorder as well disorders like osteoporosis, hypertension and others. In the case of osteoporosis, companies will typically present pictures of a top model looking her best in her mid-20s and juxtapose that image with a computer generated image of how the same person might look during her 60s or 70s with osteoporosis. On the one hand a beautiful woman, on the other a shrunken crone. The message is 'one can never be too safe'. If one wants to retain beauty and vitality it is best to monitor for osteoporosis from an early age and even treat prophylactically. In the case of bipolar disorder the risks of suicide, alcoholism, divorce, and career failure are marketed.

All of the above come together in a fifth strategy in North America – direct to consumer advertising. A now famous advertisement produced by Lilly, the makers of Zyprexa (olanzapine) begins with a vibrant woman dancing late into the night. A background voice says, "Your doctor never sees you like

[6] Accessed April 27th 2006.

this". The advert cuts to a shrunken and glum figure, and the voiceover now says, "This is who your doctor sees". Cutting again to the woman, in active shopping mode, clutching bags with the latest brand names, we hear: "That is why so many people being treated for bipolar disorder are being treated for depression and aren't getting any better – because depression is only half the story". We see the woman depressed, looking at bills that have arrived in the post before switching to seeing her again energetically painting her apartment. "That fast talking, energetic, quick tempered, up-all-night you", says the voiceover, "probably never shows up in the doctor's office".

Viewers are encouraged to log onto bipolarawareness.com, which takes them to a "Bipolar Help Center", sponsored by Lilly Pharmaceuticals. This contains a "mood disorder questionnaire".[7] In the television advert, we see our heroine logging onto bipolarawareness.com and finding this questionnaire. The voice encourages the viewer to follow her example: "Take the test you can take to your doctor, it can change your life. Getting a correct diagnosis is the first step in helping your doctor to help you".

No drugs are mentioned. The advert markets bipolar disorder. Whether this is a genuine attempt to alert people who may be suffering from a debilitating disease, or an example of disease mongering, it will reach beyond those suffering from a clearcut mood disorder to others who as a consequence will be more likely to see aspects of their personal experiences in a way that will lead to medical consultations and will shape the outcome of those consultations. "Mood-watching" like this risks transforming variations from an emotional even keel into indicators of latent or actual bipolar disorder. This advert appeared in 2002 shortly after Zyprexa had received a license for treating mania, when the company was running trials to establish olanzapine as a "mood stabilizer".

The sixth strategy involves the co-option of academia and is of particular relevance to the pediatric bipolar domain. The American Psychiatric Association meeting in San Francisco in 2003 offers a good symbol of what happened. Satellite symposia linked to the main APA meeting, as of 2000, could cost a company up to $250,000. The price of entry is too high for treatment modalities like psychotherapy. There can be up to 40 such satellites per meeting. Companies usually bring hundreds of delegates to their satellite. The satellites are ordinarily distributed across topics like depression, schizophrenia, OCD, social phobia, anxiety, dementia and ADHD. At the 2003 meeting, an unprecedented 35% of the satellites were for just one disorder – bipolar disorder.[8] These symposia have to have lecturers and a Chair,[9] and 57 senior figures in American psychiatry were involved in presenting material on bipolar disorder at these satellites, not counting other speakers on the main meeting program. One of these satellite symposia, a first ever at a major meeting, was on juvenile bipolar disorder.

The upshot of this marketing has been to alter dramatically the landscape of mental disorders. Until recently manic depressive illness was a rare disorder in the United States and Canada involving 10 per million new cases per year or 3300 new cases per year. This was a disorder that was 8 times less common than schizophrenia. In contrast bipolar disorder is now marketed as affecting 5% of the United States and Canada – that is 16.5 million North Americans, which would make it is as common as depression and 10 times more common than schizophrenia. Clinicians are being encouraged to detect and treat it. They are educated to suspect that many cases of depression, anxiety or schizophrenia may be bipolar disorder and that treatment should be adjusted accordingly [23]. And, where recently no clinicians would have accepted this disorder began before adolescence, many it seems are now prepared to accept that it can be detected in preschoolers.

[7] http://www.bipolarhelpcenter.com/resources/mdq.jsp.

[8] American Psychiatric Association (2003). Meeting Program.

[9] All of which comes with a fee, unlike symposia on the main program.

3. Bipolar disorder in children

The emergence of bipolar disorder in children needs to be reviewed against the background outlined above. Until very recently manic-depressive illness was not thought to start before the teenage years and even an adolescent onset was atypically early. The clearest indicator of change came with the publication of *The Bipolar Child* by Papolos and Papolos [35]. This sold 70,000 hardback copies in half a year. Published in January 2000, by May it was in a 10th printing. Other books followed, claiming that we were facing an epidemic of bipolar disorders in children [24] and that children needed to be treated aggressively with drugs from a young age if they were to have any hope of a normal life [12]. Newspapers throughout the United States reported increasingly on cases of bipolar children, as outlined below.

A series of books aimed at children with pastel colored scenes in fairy tale style also appeared. In *My Bipolar Roller Coaster Feelings Book* [23], a young boy called Robert tells us he has bipolar disorder. As Robert defines it doctors say you are bipolar if your feelings go to the top and bottom of the world, in roller coaster fashion. When Robert is happy he apparently hugs everybody, he starts giggling and feels like doing backflips. His parents call it bouncing off the walls. His doctor, Doctor Janet, calls it silly, giddy and goofy.

Aside from giddiness, Robert has three other features that seem to make the diagnosis of pediatric bipolar disorder. One is temper tantrums. He is shown going into the grocery store with his Mum and asking for candy. When she refuses, he gets mad and throws the bag of candy at her. His mum calls this rage and he is described as feeling bad afterwards.

Second, when he goes to bed at night Robert has nightmares. His brain goes like a movie in fast forward and he seemingly can't stop it. And third, he can be cranky. Everything irritates him – from the seams in his socks, to his sister's voice, and the smell of food cooking. This can go on to depression when he is sad and lonely, and he just wants to curl up in his bed and pull the blanket over his head. He feels as though it's the end of the world and no one cares about him. His doctor has told him that at times like this he needs to tell his parents or his doctor and he needs to get help.

Dr. Janet gives Robert medication. His view on this is that while he doesn't like having bipolar disorder, he can't change that. He also doesn't like having to take all those pills but, the bad nightmares have gone away and they help him have more good days. His father says a lot of kids have something wrong with their bodies, like asthma and diabetes and they have to take medicine and be careful, and so from this point of view he's just like many other children.

His parents have told him that his bipolar disorder is just a part of who he is, not all of who he is. That they love him and always will. Finally his doctor indicates that it's only been a little while since doctors knew that children could have bipolar disorder, and that they are working hard to help these children feel better.

In another book, *Brandon and the Bipolar Bear*, we are introduced to Brandon, who has features in common with Robert that the unwary might fail to realize indicate bipolar disorder [1]. When we are introduced to Brandon, he has just woken up from a nightmare. Second, when requested to do things that he doesn't want to do he flies into a rage. And third, he can be silly and giddy.

His mother takes both Brandon and his bear to Dr. Samuel for help, where Brandon is told that he has bipolar disorder. Dr. Samuel explains that the way we feel is controlled by chemicals in our brain. In people with bipolar disorder these chemicals can't do their job right so their feelings get jumbled inside. You might feel wonderfully happy, horribly angry, very excited, terribly sad or extremely irritated, all in the same day. This can be scary and confusing – so confusing that it can make living seem too hard.

When Brandon responds that he thinks he got bipolar disorder because he is bad, Dr. Samuel responds that many children have bipolar disorder, and they come to the doctor for help. Neither they nor Brandon are bad – it's a case of having an illness that makes you feel bad.

Brandon moves on to asking how he got bipolar disorder if he didn't get it from being bad, to which Dr. Samuel responds by asking him how he got his green eyes and brown hair. Brandon and his mother respond that these came from his parents. And Dr. Samuel tells them it's the same with bipolar disorder. That it can be inherited. That someone else in the family may have it also.

The final exchange involves Brandon asking whether he will ever feel better. Dr. Samuel response is upbeat – there are now good medicines to help people with bipolar disorder, and that Brandon can start by taking one right away. Brandon is asked to promise that he will take his medicine when told by his mother.

Brandon and the Bipolar Bear comes with an associated coloring book, in which Brandon's Dad makes it clear that a lot of kids have things wrong with their bodies, like asthma and diabetes, and they have to take medicine and be careful too.

Janice Papolos, co-author of *The Bipolar Child*, in a review on the back cover of Brandon and the Bipolar Bear says: 'children will follow (and relate to) Brandon's experience with rapid mood swings, irritability, his sense of always being uncomfortable and his sadness that 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 that the medicine will make him feel better. We were so moved by the power of this little book and we feel better that we can now highly recommend a book for children aged 4 through 11'.

The book *The Bipolar Child* arrived at Sheri Lee Norris' home in Hurst, Texas, in February 2000. When it did Karen Brooks, a reporter in the Dallas Star-Telegram describes Norris as tearing open the package with a familiar mix of emotions. Hope, skepticism, fear, guilt, shame, love. But as she reads in the book about violent rages, animal abuse, inability to feel pain, self-abuse and erratic sleeping patterns, Norris is reported as feeling relief for the first time in over a year. Now she finally knew what was wrong with her daughter... Within days, Heather Norris, then 2, became the youngest child in Tarrant County with a diagnosis of bipolar disorder [5].

Brooks goes on to note that families with mentally ill children are plagued with insurance woes, a lack of treatment options and weak support systems but that parents of the very young face additional challenges. It is particularly hard to get the proper diagnosis and treatment because there has been scant research into childhood mental illness and drug treatments to combat them. Routine childcare is difficult to find, because day-care centers, worried about the effect on other children, won't accept mentally ill children or will remove them when they are aggressive. Few baby sitters have the expertise or the desire to handle difficult children, leaving parents with little choice but to quit work or work from home.

Having outlined these difficulties, Brooks also notes that the lack of public awareness of childhood mental illness means that parents are judged when their children behave badly. They are accused of being poor parents, of failing to discipline their children properly, or even of sexual or physical abuse or neglect. The sense of hopelessness is aggravated when they hear about mentally ill adults; this leaves them wondering whether the battles they and their children are fighting will go on forever.

In a few short paragraphs here Brooks outlines the once and future dynamics of disease from ancient to modern times – the reflection on parents or family, the concerns for the future, the hope for an intervention. But she also covers a set of modern and specifically American dynamics. Heather Norris's problems began with temper tantrums at 18 months old. Sheri-Lee Norris had a visit from the Child Protective Services. Someone had turned her in because Heather behaved abnormally. Sheri-Lee was furious and felt betrayed. She brought Heather to pediatricians, play therapists and psychiatrists, where

Heather was diagnosed with ADHD and given Ritalin. This made everything worse. Faced with all this, a psychiatrist did not make the diagnosis of bipolar disorder because the family had no history of it. But Sheri-Lee began asking relatives and discovered that mental illness was, indeed, in her family's history. She presented that information along with a copy of *The Bipolar Child* to her psychiatrist, and Heather got a diagnosis of bipolar disorder immediately.

Heather Norris' story is not unusual. The mania for diagnosing bipolar disorders in children hit the front cover of *Time* in August 2002, which featured 9-year-old Ian Palmer and a cover title Young and Bipolar [26], with a strapline, why are so many kids being diagnosed with the disorder, once known as manic-depression? The Time article and other articles report surveys that show 20% of adolescents nationwide have some form of diagnosable mental disorder. Ian Palmer, we are told, just like Heather Norris, had begun treatment early – at the age of 3 – but failed to respond to either Prozac or stimulants, and was now on anticonvulsants.

While Heather Norris was in 2000 the youngest child in Tarrant County to be diagnosed as bipolar, Papolos and Papolos in *The Bipolar Child* indicate that many of the mothers they interviewed for their book remembered their baby's excessive activity *in utero*, and the authors seem happy to draw continuities between this and later bipolar disorder. The excessive activity amounts to hard kicking, rolling and tumbling and then later keeping the ward awake with screaming when born. Or in some instances being told by the sonographer and obstetrician that it was difficult to get a picture of the baby's face or to sample the amniotic fluid because of constant, unpredictable activity [35]. It is not unusual to meet clinicians who take such reports seriously.

Anyone searching the Internet for information on bipolar disorder in children are now likely to land at BPChildren.com, run by Tracy Anglada and other co-authors of the books mentioned above. Or at the Juvenile Bipolar Research Foundation (JBRF), linked to the Papoloses and *The Bipolar Child*. Or at a third site, bpkids.org, linked to a Child and Adolescent Bipolar Foundation, which is supported by unrestricted educational grants from major pharmaceutical companies.

In common with the mood-watching questionnaires in the adult field, all three sites offer mood-watching questionnaires for children. The Juvenile Bipolar Research Foundation has a 65-item Child Bipolar Questionnaire, which also featured in the *Time* magazine piece above; on this scale most normal children would score at least modestly.[10]

The growing newsworthiness of childhood bipolar disorder also hit the editorial columns of the American Journal of Psychiatry in 2002 [40]. But where one might have expected academia to act as a brake on this new enthusiasm, its role has been in fact quite the opposite.

4. The academic voice

As outlined above until very recently manic-depressive illness was not thought to start before the teenage years. The standard view stemmed from Theodore Ziehen, who in the early years of the 20th century established, against opposition, that it was possible for the illness to start in adolescence [3]. This was the received wisdom for 100 years.

As of 2006, European articles on the issue of pre-pubertal bipolar disorder continued to express agnosticism as to whether there was such an entity [28]. The view was that patterns of overactivity could be seen in patients with learning disabilities/mental retardation, or for example in Asberger's syndrome, but it was not clear that these should be regarded as indicative of manic-depressive disease.

[10] www.jbrf.org/cbq/cbq_survey.cfm. Accessed December 1st 2005.

Geller and colleagues in St. Louis framed the first set of criteria for possible bipolar disorder in children in 1996 as part of an NIMH funded study [13]. Using these criteria the first studies reporting in 2002 suggested that essentially very little was known about the condition. There were children who might meet the criteria, but these had a very severe condition that in other circumstances have been likely to be diagnosed as childhood schizophrenia or else they displayed patterns of overactivity against a background of mental retardation [14].

The course of this study and the entire debate had however been derailed by the time the Geller study reported. In 1996, a paper from an influential group, based at Massachusetts' General Hospital, working primarily on ADHD, suggested there were patients who might appear to have ADHD who in fact had mania or bipolar disorder [4,11]. This study had used lay raters, did not interview the children about themselves, did not use prepubertal age specific mania items, and used an instrument designed for studying the epidemiology of ADHD. Nevertheless the message stuck. Cases of bipolar disorder were being misdiagnosed as ADHD. Given the many children diagnosed with ADHD who do not respond to stimulants, and who are already in the treatment system, this was a potent message for clinicians casting round for some other option.

A further study by Lewinsohn and colleagues in 2000 added fuel to the fire [29]. Even though this study primarily involved adolescents and pointed toward ill-defined overactivity rather than proper bipolar disorder, the message that came out was that there was a greater frequency of bipolar disorder in minors that had been previously suspected.

These developments led in 2001 to an NIMH roundtable meeting on prepubertal bipolar disorder [34] to discuss the issues further. But by then any meeting or publication, even one skeptical in tone, was likely to add fuel to the fire. Simply talking about pediatric bipolar disorder endorsed it. The Juvenile Bipolar Research Foundation website around this time noted that bipolar disorder in children simply does not look like bipolar disorder in adults, in that children's moods swing several times a day – they do not show the several weeks or months of elevated mood found in adults. They baldly state that "The DSM needs to be updated to reflect what the illness looks like in childhood".[11]

The Child and Adolescent Bipolar Foundation convened a meeting and treatment guideline process in July 2003 that was supported by unrestricted educational grants from Abbott Astra-Zeneca, Eli Lilly, Forrest, Janssen, Novartis and Pfizer. This assumed the widespread existence of pediatric bipolar disorder and the need to map out treatment algorithms involving cocktails of multiple drugs [27].

There are many ambiguities here. First is the willingness it seems of all parties to set aside all evidence from adult manic-depressive illness which involves mood states that persist for weeks or months and argue that children's moods may oscillate rapidly, up to several times per day, while still holding the position that this disorder is in some way continuous with the adult illness and therefore by extrapolation should be treated with the drugs used for adults.

Another ambiguity that the framers of the American position fail to advert to is a problem with DSM-IV. Advocates of pediatric bipolar disorder repeatedly point to problems with DSM-IV that hold them back from making diagnoses. But in fact, DSM-IV is more permissive than the rest of world in requiring a diagnosis of bipolar disorder following a manic episode – in practice any sustained episode of overactivity. The International Classification of Disease in contrast allows several manic episodes to be diagnosed without a commitment to the diagnosis of bipolar disorder. The rest of the world believes it simply does not know enough even about the relatively well understood adult illness to achieve diagnostic consistency worldwide. DSM-IV in fact therefore makes it easier to diagnose bipolar disorder

[11] www.jbrf.org/juv_bipolar/faq.html. Accessed December 1st 2005.

than any other classification system, but therapeutic enthusiasts want an even further loosening of these already lax criteria.

Finally, we appear to have entered a world of operational criteria by proxy. Clinicians making these diagnoses are not making diagnoses based on publicly visible signs in the patients in front of them, or publicly demonstrable on diagnostic tests, as is traditional in medicine. Nor are they making the diagnoses based on what their patients say, as has been standard in adult psychiatry, but rather these are diagnoses made on the basis of what third parties, such as parents or teachers, say without apparently any method to assess the range of influences that might trigger parents or teachers to say such things – the range of influences brought out vividly by Karen Brooks in her Star-Telegram articles.

When clinicians raise just this point [17], the response has been aggressive. "Mood need not be elevated, irritable etc. for a week to fulfill criteria... A period of 4 days suffices for hypomania. This is... itself an arbitrary figure under scrutiny... Dr. Harris is incorrect... that the prevalence of adult bipolar disorder is only 1–2%. When all variants are considered the disease is likely to be present in more than 6% of the adult pop. There are still those who will not accept that children commonly suffer from bipolar illness regardless of how weighty the evidence. One cannot help but wonder whether there are not political and economic reasons for this stubborn refusal to allow the outmoded way of thought articulated by Dr. Harris to die a peaceful death. It is a disservice to our patients to do otherwise" [9].

Where one might have thought some of the more distinguished institutions would bring a skeptical note to bear on this, they appear instead to be fueling the fire. Massachusetts's General Hospital (MGH) have run trials of the antipsychotics risperidone and olanzapine on children with a mean age of 4 years old [30,31]. A mean age of 4 all but guarantees three and possibly two year olds have been recruited to these studies.

MGH in fact recruited juvenile subjects for these trials by running its own DTC adverts featuring clinicians and parents alerting parents to the fact that difficult and aggressive behavior in children aged 4 and up might stem from bipolar disorder. Given that it is all but impossible for a short term trial of sedative agents in pediatric states characterized by overactivity not to show some rating scale changes that can be regarded as beneficial, the research can only cement the apparent reality of juvenile bipolar disorder into place.

As a result where it is still rare for clinicians elsewhere in the world to make the diagnosis of manic-depressive illness before patients reach their mid to late teens, drugs like olanzapine and risperidone are now in extensive and increasing use for children including preschoolers in America with relatively little questioning of this development [7].

Studies run by academics that apparently display some benefits for a compound have possibly become even more attractive to pharmaceutical companies than submitting the data to the FDA in order to seek a license for the treatment of children. Companies can rely on clinicians to follow a lead given by academics speaking on meeting platforms or in published articles. The first satellite symposium on juvenile bipolar disorder at a major mainstream meeting, the American Psychiatric Association meeting in 2003 featured the distinguished clinical faculty of MGH. The symposium was supported by an unrestricted educational grant. None of the speakers will have been asked to say anything other than what they would have said in any event. The power of companies does not lie in dictating what a speaker will say but in providing platforms for particular views. If significant numbers of clinicians in the audience are persuaded by what distinguished experts say, companies may not need to submit data to FDA and risk having lawyers or others pry through their archives to see what the actual results of studies look like. As an additional benefit, academics come a lot cheaper than putting a sales force in the field.

It would seem only a matter of time before this American trend spreads to the rest of the world. In a set of guidelines on bipolar disorder issued in 2006, Britain's National Institute of Health and Clinical Excellence (NICE), which is widely regarded as being completely independent of the pharmaceutical industry, has a section on children and adolescents [33]. The guideline contains this section because if there are treatment studies on a topic, NICE has to perforce consider them; it cannot make the point that hitherto unanimous clinical opinion has held that bipolar disorders do not start in childhood. But simply by considering the treatment for bipolar disorders in childhood, NICE effectively brings it into existence, illustrating in the process the ability of companies to capture guidelines (Healy D., submitted). And again, the need for a company to seek an indication for treatment in children recedes if influential guidelines tacitly endorse such treatment.

5. Munchausen's syndrome new variant?

As outlined above, a number of forces appear to have swept aside traditional academic skepticism with the result that an increasing number of children and infants are being put on cocktails of potent drugs without any evidence of benefit.

One of the features of the story is how a comparatively few players have been able to effect an extraordinary change. There the academics noted above and a handful of others. One was Robert Post who was among the first to propose that anticonvulsants might be useful for adult manic-depressive disease, who when the frequency of the disorder began to increase rather than decrease as usually happens when treatments work, promoted the idea that the reason we were failing was because we had failed to catch affected individuals early enough. No age was too early.

> One would encourage major efforts at earlier recognition and treatment of this potentially incapacitating and lethal recurrent central nervous system disorder. It would be hoped that instituting such early, effective, and sustained prophylactic intervention would not only lessen illness-related morbidity over this interval, but also change the course of illness toward a better trajectory and more favorable prognosis [36].

Another group consists of evangelical parents and clinicians, who bring to the process of proselytizing about bipolar disorder a real fervor. Some of these parents and clinicians readily contemplate the possibility of making a diagnosis *in utero*. When those challenging such viewpoints are subject to opprobrium, one has to ask what has happened to the academic voices that should be questioning what is happening here.

Finally there is the role of companies who make available the psychoactive drugs without which the diagnoses would not be made, unrestricted educational grants, and access to academic platforms. This has clearly facilitated the process outlined above. While companies cannot market directly to children, it is now clear that documents from 1997 show that at least one company was aware of the commercial opportunities offered by juvenile bipolar disorder [39].

If the process outlined here was one that could reasonably be expected to lead to benefits it could regarded as therapeutic. But given that there is no evidence for benefit and abundant prima facie evidence that giving the drugs in question to vulnerable subjects in such quantities cannot but produce consequent difficulties for many of these minors, one has to wonder whether we are not witnessing instead a variation on Munchausen's syndrome, where some significant other wants the individual to be ill and these significant others derive some gain from these proxy illnesses.

The contrast between the developing situation and the historical record is striking. The records of all admissions to the asylum in North Wales from North West Wales for the years from 1875 to 1924 show that close to 3,500 individuals were admitted, from a population base of slightly more than a quarter of a million per annum (12,500,000 person years). Of these, only 123 individuals were admitted for manic-depressive disease. The youngest admission for manic-depression was aged 17. The youngest age of onset may have been EJ, who was first admitted in 1921 at the age of 26, but whose admission record notes that she "has had several slight attacks in the last 12 years, since 13 years of age". All told there were 12 individuals in 50 years with a clear onset of illness under the age of 20 [18]. But it would seem almost inevitable that there will be a greater frequency of hospital admissions for juveniles in future diagnosed with bipolar disorder. This is not what ordinarily happens when medical treatments work.

Competing interests

J. Le Noury has no competing interests.

In the past 10 years D. Healy has had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for or been in receipt of support to attend meetings from Astra-Zeneca, Boots/Knoll Pharmaceuticals, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, Sanofi, SmithKline Beecham, Solvay. In the past two years, he has had lecture fees and support to attend meetings from Astra-Zeneca and Lundbeck.

In the past ten years D. Healy has been an expert witness for the plaintiff in 15 legal actions involving SSRIs and has been consulted on a number of attempted suicide, suicide and suicide-homicide cases following antidepressant medication, in most of which he has offered the view that the treatment was not involved. He has been an expert witness for the NHS in a series of therapy (LSD/ECT) related cases, and in one patent case.

References

[1] T. Anglada, *Brandon and the Bipolar Bear*, Trafford Publishing, Victoria, BC, 2004.
[2] K. Applbaum, *The Marketing Era*, Routledge, New York, 2004.
[3] C. Baethge, R. Glovinsky and R.J. Baldessarini, Manic-depressive illness in children: an early twentieth century view by Theodore Ziehen (1862–1950), *Hist. Psychiatr.* **15** (2004), 201–226.
[4] J. Biederman, S. Faraone, E. Mick, J. Wozniak, L. Chen, C. Ouellette, A. Marrs, P. Moore, J. Garcia, D. Mennin and E. Lelon, Attention-deficit hyperactivity disorder and juvenile mania: an overlooked co-morbidity?, *J. Am. Acad. Child Adolesc. Psychiatr.* **35** (1996), 997–1008.
[5] K. Brooks, No Small Burden, Families with mentally ill children confront health care shortcomings, undeserved stigma of 'bad parenting', Dallas Star Telegram, July 19th, 2000, DOI: 1%3A00MENTALHEALTH170719100.html.
[6] C.W. Colton and R.W. Manderscheid, Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states, *Prev. Chronic Dis.* (2006). Available from: http://www.cdc.gov/pcd/issues/2006/apr/05_0180.htm.
[7] W. Cooper, P.G. Arbogast, H. Ding, G.B. Hickson, C. Fuchs and W.A. Ray, Trends in prescribing of antipsychotic medications for US children, *Ambul. Pediatr.* **6** (2006), 79–83.
[8] M. De Hert, E. Thys, G. Magiels and S. Wyckaert, *Anything or Nothing. Self-Guide for People with Bipolar Disorder*, Uitgeverij Houtekiet, Antwerp, 2005.
[9] S. Dilsaver, Review of J. Harris, *J. Bipolar Disorders* **4** (2005), 8–9.
[10] C.L. Ernst and J.F. Goldberg, The reproductive safety profile of mood-stabilizers, atypical antipsychotics and broad-spectrum psychotropics, *J. Clin. Psychiatr.* **63**(Suppl. 4) (2002), 42–55.
[11] S.V. Faraone, J. Biederman, D. Mennin, J. Wozniak and T. Spencer, Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype?, *J. Am. Acad. Child. Adolesc. Psychiatr.* **36** (1997), 1378–1387.

[12] R.L. Findling, R.A. Kowatch and R.M. Post, *Pediatric Bipolar Disorder. A Handbook for Clinicians*, Martin Dunitz, London, 2003.
[13] B. Geller, M. Williams, B. Zimmerman and J. Frazier, Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (Wash-U-KSADS), Washington University, St. Louis, 1996.
[14] B. Geller, J. Craney, K. Bolhoffer, M.P. DelBello, D. Axelson, J. Luby, M. Williams, B. Zimerman, M.J. Nickelsburg, J. Frazier and L. Beringer, Phenomenology and longitudinal course of children with a prepubertal and early adolescent bipolar disorder phenotype, in: *Bipolar Disorder in Childhood and Early Adolescence*, B. Geller and M.P. DelBello, eds, The Guilford Press, New York, 2003, pp. 25–50.
[15] S.N. Ghaemi, On defining 'mood stabilizer', *Bipolar Disorder* **3** (2001), 154–158.
[16] F.K. Goodwin and K.R. Jamison, *Manic Depressive Illness*, Oxford University Press, New York, 1990.
[17] J. Harris, The increased diagnosis of juvenile "bipolar disorder", what are we treating?, *Psychiatr. Serv.* **56** (2005), 529–531.
[18] M. Harris, S. Chandran, N. Chakroborty and D. Healy, Service utilization in bipolar disorders, 1890 and 1990 compared, *Hist. Psychiatr.* **16** (2005), 423–434.
[19] D. Healy, *The Creation of Psychopharmacology*, Harvard University Press, Cambridge, MA, 2002.
[20] D. Healy, *Let Them Eat Prozac*, New York University Press, New York, 2004, Chapter 4.
[21] D. Healy, The Latest Mania. Selling Bipolar Disorder, *PloS Medicine* (2006), http://dx.doi.org/10.1371/journal.pmed.0030185.
[22] D. Healy, *Mania*, Johns Hopkins University Press, Baltimore, MD, 2008.
[23] B. Hebert, *My Bipolar Roller Coaster Feeling Book*, Trafford Publishing, Victoria, BC, 2005.
[24] G. Isaac, *Bipolar not ADHD. Unrecognized Epidemic of Manic-Depressive Illness in Children*, Writers' Club Press, Lincoln, NE, 2001.
[25] M. Joukamaa, M. Heliovaara, P. Knekt, A. Aromaa, R. Partosalo and R. Lehtinen, Schizophrenia, neuroleptic medication and mortality, *Br. J. Psychiatr.* **188** (2006), 122–127.
[26] J. Kluger and S. Song, Young and Bipolar. Once called Manic Depression, the disorder afflicted adults. Now it's striking kids. Why?, *TIME Magazine* **160** (2002), 30–41.
[27] R.A. Kowatch, M. Fristad, B. Birmaher, K.D. Wagner, R.L. Findling, M. Hellander and The Child Psychiatric Workgroup on Bipolar Disorder, Treatment guidelines for children and adolescents with bipolar disorder, *J. Am. Acad. Child Adolesc. Psychiatr.* **44** (2005), 213–235.
[28] Z.A. Kyte, G.A. Carlsson and I.M. Goodyer, Clinical and neuropsychological characteristics of child and adolescent bipolar disorder, *Psychol. Med.* **36** (2006), 1197–1211.
[29] P. Lewinsohn, D. Klein and J. Seeley, Bipolar disorder during adolescence and young adulthood in a community sample, *Bipolar Disorder* **2** (2000), 281–293.
[30] E. Mick, J. Biederman, M. Dougherty and M. Aleardi, Comparative efficacy of atypical antipsychotics for pediatric bipolar disorder [abstract], *Acta Psychiatr. Scand.* **110** (2004), P50, 29.
[31] E. Mick, J. Biederman, M. Dougherty and M. Aleardi, Open trial of atypical antipsychotics in pre-schoolers with bipolar disorder [abstract], *Acta Psychiatr. Scand.* **110** (2004), P51, 29.
[32] R. Moynihan and A. Cassels, *Selling Sickness*, Nation Books, New York, 2005.
[33] National Institute for Health & Clinical Excellence (NICE), Bipolar disorder, *Clinical Guideline* 38, 2006. Available on www.nice.org.uk.
[34] National Institute of Mental Health Research Roundtable on Prepubertal Bipolar Disorder, *J. Am. Acad. Child Adolesc. Psychiat.* **40** (2001), 871–878.
[35] D. Papolos and J. Papolos, *The Bipolar Child*, Random House, New York, 2000.
[36] R.M. Post, Treatment resistance in bipolar disorder, in: *Royal College of Psychiatrists Meeting*, Newcastle, England, October 17th, 2002.
[37] Psychopharmacologic Drugs Advisory Committee, in: *Forty-Fourth Meeting*, NDA 20-320: Depakote, Transcript of Proceedings, Department of Health and Human Services, Washington, DC, February 6th, 1995.
[38] J.G. Storosum, T. Wohlfarth, C.C. Gispen-de Wied, D.H. Linszen, B.P. Gersons, B. van Zwieten and W. van den Brink, Suicide-risk in placebo controlled trials of treatment for acute manic episode and prevention of manic-depressive episode, *Am. J. Psychiatr.* **162** (2005), 799–802.
[39] G.D. Tollefson, Zyprexa Product Team: 4 Column Summary. Zyprexa MultiDistrict Litigation 1596, Document ZY200270343, 1997.
[40] F.R. Volkmar, Changing perspectives on mood disorders in children, *Am. J. Psychiatr.* **159** (2002), 893–894.