Poles apart

There's a huge gap between the claims made for "mood stabilising" drugs and the evidence for their safety and effectiveness. So why are we now dishing them out even to young children, asks psychiatrist **David Healy**, who helped uncover the suicide risks associated with modern antidepressants

IT STARTS with a vibrant woman dancing late into the night. "Your doctor never sees you like this," a voice-over says. The screen cuts to a shrunken, glum figure: "This is who your doctor sees." Next we see the woman in active shopping mode. "That is why so many people with bipolar disorder are being treated for depression and aren't getting any better – because depression is only half the story." We see the woman again depressed, looking at bills that have arrived in the post, then cut to her energetically painting her apartment. "That fast-talking, energetic, quick-tempered, up-all-night you," says the voice-over, "probably never shows up in the doctor's office."

This advertisement was screened on US television in 2002. It encouraged viewers to log onto bipolarawareness.com, which takes you to a website called the Bipolar Help Center. Scroll down and you see the site belongs to pharmaceutical company Eli Lilly. Here you will find a "mood disorder questionnaire". In the TV ad, we see our heroine filling in this questionnaire, and the ad encourages viewers 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 treating bipolar disorder. Help your doctor to help you."

This ad markets bipolar disorder. It can be seen as a genuine attempt to alert people who are unaware that they are suffering from one of the most debilitating and serious psychiatric diseases: manic-depressive illness, in which people undergo periods of extreme emotional lows and periods of extreme highs that can wreck lives.

The ad can also be seen as an example of disease mongering: selling a disease so you can sell treatments for it. It encourages people to view any variations from an even emotional keel as signs of an illness that requires treatment. While it does not mention any drugs, the website stresses the importance of long-term medication. At the time the ad was aired, Eli Lilly's drug olanzapine (Zyprexa) had just been approved by the US Food and Drug Administration for treating periods of mania, and the company was running trials aimed at establishing olanzapine as a "mood stabiliser".

Before 1995, the term "mood stabilisers" had barely been heard of. So what exactly are these drugs, and how effective and safe are they?

From the 1950s on, the depressions of manic-depressive illness were treated with antidepressants, and the manias with the drugs known as antipsychotics. Because doctors did not rush to take people off these drugs after episodes of illness, many patients remained on them for years. However, the only agent thought to prevent episodes of manic-depressive illness if taken on a permanent basis was lithium, a cheap trace element, though it was not originally referred to as a "mood stabiliser".

> "There is a surge of diagnoses of bipolar disorder in children. Drugs are given to preschoolers"

The drugs first described as "mood stabilisers" were anticonvulsants, a group used for treating epilepsy. Epileptic fits can cause changes in the brain that make future fits more likely – an effect called "kindling" – and it was once widely believed that anticonvulsants reduce or "quench" these changes. In the 1980s, Robert Post of the US National Institute of Mental Health suggested that anticonvulsants might stabilise moods by a comparable "quenching" effect – in other words, that long-term treatment with anticonvulsants might prevent an episode of mood disorder "kindling" future episodes.

Although anticonvulsants had occasionally been used for treating bipolar disorders, there was at the time little evidence of a preventive effect to support this analogy. Nevertheless, the idea that some drugs might stabilise moods appealed to doctors and their patients. It was also very attractive to pharmaceutical companies, which were starting to take an interest in the market for bipolar drugs.

Bipolar disorders entered the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1980. The criteria for bipolar I disorder (classic manic-depressive illness) included an episode of hospitalisation for mania. Since then, mood disorders that do not require hospitalisation have been described, such as bipolar II disorder, bipolar disorders NOS (not otherwise specified) and cyclothymia. With the emergence of these so-called "community" disorders, estimates for the prevalence of bipolar disorders have risen from 0.1 per cent of the population to 5 per cent or more. Along with this expansion in estimated prevalence – and in the market for drugs – have come new journals and a slew of bipolar societies and annual conferences, many heavily funded by drug companies.

In the industry's hands, the growth of awareness of "mood stabilisation" has been

GARY SAWYER

sensational. It started in 1995, the year the FDA granted Abbott Laboratories a licence to use the anticonvulsant sodium valproate (Depakote) to treat periods of mania. In the US, approval allows companies to advertise drugs for the licensed purpose, and in its ads for doctors Abbott described valproate as a "mood stabiliser" – a label that may have encouraged many to think it could do more than treat manias.

By 2001, this term featured in the titles or abstracts of more than 100 scientific papers a year (see Graph, page 40), and it has started to be applied to some antipsychotic drugs as well as to anticonvulsants like sodium valproate. Yet until 2000 no companies making antipsychotics had sought a licence for using these drugs as a "maintenance" treatment. What's more, academic review articles make it clear that there is still no consensus among psychiatrists on what a "mood stabiliser" is.

There has always been a rationale to using antipsychotics to treat the periods of mania that people with bipolar disorder go through. There is, however, no consensus on a theoretical rationale for the use of antipsychotics as a long-term treatment for bipolar disorder, and scant evidence of their effectiveness. Nevertheless, from 2000 onwards, Eli Lilly, Janssen and AstraZeneca, the makers of the antipsychotics olanzapine, risperidone (Risperdal) and quetiapine (Seroquel) respectively, marched in on this new territory and began the process of getting approval for using these drugs not just to treat mania but as long-term "mood stabilisers".

The result of these trends is that people with a bipolar disorder are now routinely prescribed a cocktail of expensive drugs on ▶

a permanent basis. Drug companies, often with the enthusiastic support of psychiatrists, have managed to firmly establish the idea that these disorders require lifelong preventive medication, not merely treatment for episodes of mania or depression.

For instance, Eli Lilly's Bipolar Help Center website states: "Staying on medication over the long haul is critical. Without it, symptoms will reappear and the illness will get worse." Similarly, information available from Janssen, the maker of Risperdal, states: "Medicines are crucially important in the treatment of bipolar disorders. Studies over the past twenty years have shown beyond the shadow of doubt that people who receive the appropriate drugs are better off in the long term than those who receive no medicine."

There is, however, much less evidence than many might think to support these claims. In the case of the community disorders now being pulled into the manic-depressive net, there is almost none at all, as drug trials have mostly involved people diagnosed with bipolar I disorder.

In fact, with the possible exception of lithium for bipolar I disorder, no randomised controlled trials show that patients with bipolar disorders who receive drugs do better in the long term than those who receive no medicine. Eli Lilly's olanzapine was approved by the FDA for the long-term treatment of bipolar I disorder in January 2004 on the basis of a randomised, placebo-controlled trial. But this trial essentially lasted only a year, and most apparent relapses occurred just after patients stopped taking olanzapine, which suggests that they were in fact suffering withdrawal symptoms. Even in the case of lithium, there is some dispute over what has been demonstrated.

It is true that this lack of evidence may stem in part from difficulties in conducting trials that last more than a few weeks for conditions as complex as manic-depressive illness. However, the existing evidence of benefit for one agent (lithium) and possible benefit for one more (olanzapine) must be weighed against the dangers. The potential toxicity of lithium is well known, and a consistent body of evidence shows that people undergoing regular, long-term treatment with antipsychotics have an increased risk of death. This and other known side effects of antipsychotics do not show up in the relatively short-term trials aimed at demonstrating treatment effects in psychiatry. There is also evidence from trials of antipsychotics for schizophrenia that there are significantly more suicides among those receiving the active drug than those on placebo.

There are also grounds for questioning whether the benefits supposedly demonstrated in clinical trials translate into therapeutic efficacy. In north Wales a century ago, patients with bipolar I disorder had on average four hospital admissions every 10 years. Today, despite dramatic improvements in services and treatment with the very latest drugs, bipolar I patients are admitted four times as often (*History of Psychiatry*, vol 16, p 423). This is not ordinarily what happens when treatments "work", but quite often is what happens when treatments have side effects.

Fearsome toll

Those selling bipolar disorder stress the disorder's fearsome toll in terms of suicides. Indeed, controversy over the role of antidepressants in triggering suicide has been recast by some as a result of mistaken diagnosis: if the doctor had only realised the patient was bipolar, the argument goes, they would not have mistakenly prescribed an antidepressant. Because of this suicide risk, most psychiatrists would find it difficult not to prescribe drugs for any person with bipolar disorder. Yet as real as this risk is, the best available evidence shows that medication does not help.

Jitschak Storosum of the Medicines Evaluation Board of the Netherlands and colleagues analysed all four placebo-controlled, double-blind, randomised trials of "mood stabilisers" for the prevention of manic-depressive episodes submitted to the board between 1997 and 2003 (*The American Journal of Psychiatry*, vol 162, p 799). They compared the suicide risk in patients on various drugs with those on placebo. Two suicides (equivalent to 493 per 100,000 person-years of drug exposure) and eight suicide attempts (1969 per 100,000 person-years of exposure) occurred in the 943 patients given an active drug. No suicides and two suicide attempts (1467 per 100,000 person-years of exposure) occurred in 418 patients on placebo. Based on these figures, I calculate that suicidal acts are 2.2 times as likely in those taking "mood stabilisers" compared with those on placebo.

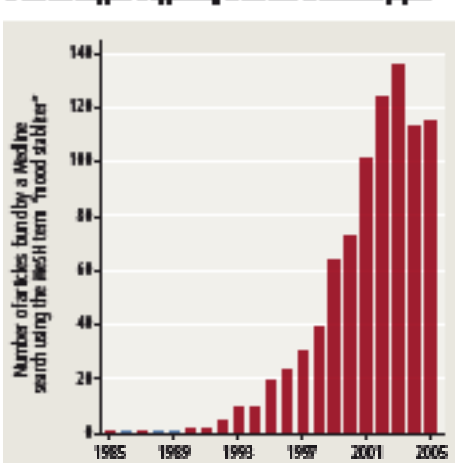
> "Suicidal acts are twice as likely in bipolar patients on mood stabilisers"

If the efficacy of "mood stabilisers" is questionable while their dangers might include an increased risk of suicide, we should surely be very cautious about expanding their use. Yet in the US there is now a surge of diagnoses of bipolar disorder in children despite the facts that these children do not meet the usual criteria for bipolar I disorder and that until recently the general wisdom was that it was very rare for manic-depressive illness to start in the pre-teen years.

This trend is exemplified by the book *The Bipolar Child* by Demitri and Janice Papolos. Published in 2000, it sold 70,000 hardback copies in six months in the US. As the *Star-Telegram* newspaper in Fort Worth, Texas, reported in July 2000, *The Bipolar Child* made all the difference to a local girl, Heather Norris, then aged 2. Heather had been diagnosed with attention deficit hyperactivity disorder (ADHD), treatment of which seemed to be making her worse. After reading *The Bipolar Child*, her mother challenged her doctor to change the diagnosis – and the medication.

The book's authors have senior positions in a charity called the Juvenile Bipolar Research Foundation, whose sponsors include drug company Novartis. The charity's FAQ on what it calls "early onset" bipolar disorder states: "Adults seem to experience abnormally intense moods for weeks or months at a time, but children appear to experience such rapid shifts of mood that they commonly cycle many times within the day."

ALL THE RAGE

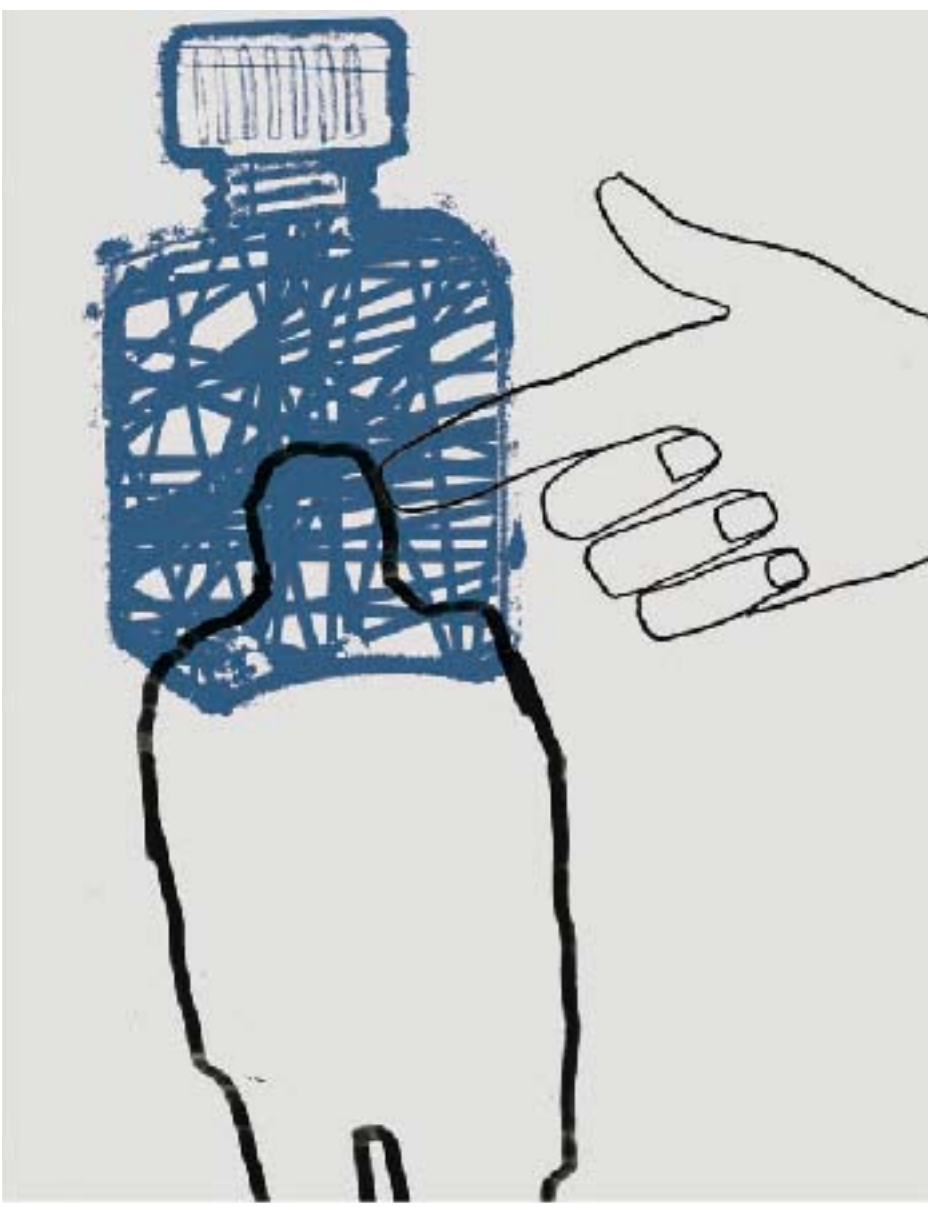


If we consider adults alone for a moment, there is already potential for creating an "epidemic" of bipolar disorder because people are being diagnosed based on criteria that depend upon subjective judgements rather than any objective criterion of disability, such as hospitalisation or being off work for a month. With children, the risk is even greater because diagnosis is based mainly on the reports of parents, with little scope in most clinical practice for critical scrutiny of the social forces influencing parenting. For instance, in an age in which both parents often have to work long hours and childcare centres reject "difficult" children, medication may be the easiest way to deal with behavioural problems.

Experts who appear willing to go so far as to accept the possibility that the first signs of bipolar disorder may be patterns of overactivity in utero can only compound these problems. If bipolar diagnoses in children were solely for research purposes, there might be little problem. However, drugs such as olanzapine and risperidone are now being given to preschoolers in the US.

Some research on the subject is adding fuel to the fire. What might once have been thought of as sober institutions, such as Massachusetts General Hospital in Boston, have run trials of olanzapine and risperidone on children with an average age of 4. The hospital recruited participants by running TV ads stating that difficult and aggressive behaviour in children aged 4 and up can stem from bipolar disorder. The ad does more than recruit children with a clear disorder: it suggests that everyday behavioural difficulties may be better seen in terms of a disorder. Given that bipolar disorder in children is all but unrecognised outside the US, it seems likely that a significant proportion of these children will not meet the conventional criteria for bipolar I disorder.

"The research appears predestined to confirm the diagnosis"



It is all but impossible for a short-term trial of sedative agents for treating any sort of state that involves periods of overactivity not to show some rating-scale changes that can be regarded as beneficial. This research thus appears predestined to validate the diagnosis and thus increase the pressure for treatment.

Several years after Heather Norris was diagnosed with bipolar disorder, the original rationale for mood stabilisation was greatly weakened by the results of the largest ever randomised trial of immediate versus deferred anticonvulsant therapy for people who had experienced a single seizure. The trial found that although immediate anti-epileptic drug treatment reduces the occurrence of seizures in the next one to two years, such treatment does not affect long-term remission in individuals with single or infrequent seizures. Yet the entire concept of "mood stabilisation" was based on an analogy with epilepsy, not on any demonstrations of long-term benefit of any particular drug.

The use of "mood stabilisers" as a long-term maintenance treatment for bipolar disorders is based more on wishful thinking than on a solid theoretical or empirical basis. There is good evidence that these drugs threaten the health and lives of adults taking them – who knows what lies in store for the growing number of young children given these complex agents? Only the health of drug companies' profit margins appears assured. ●

David Healy is a psychiatrist at the North Wales Department of Psychological Medicine, Cardiff University, UK. This is an edited version of an essay in *PLoS Medicine*, one of a series of articles on disease mongering available at http://collections.plos.org/diseasemongering-2006.php