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The US has seen a decade of successful litigation against the manufacturers of antidepressants – drugs that caused their users to commit homicide and suicide, often violent and multiple. These are manifestations of an acknowledged side-effect, akathisia.

# PHARMA FRAUD, PHARMACOLOGICAL IATROGENESIS AND THE CRISIS IN MENTAL HEALTH

By Dr Yolande Lucire

**T**he required causal relationship between the drug and the behaviour has been firmly established by epidemiological evidence in six Daubert Hearings.<sup>1</sup> On orders from these courts, the drug companies had to open their archives to Professor David Healy, who uncovered systematic non-disclosure of 'serious adverse drug events' (ADEs); that is, debilitating physical and mental side-effects, including suicide and sudden death.

Healy and Whitaker jointly published 'Antidepressants and Suicide: Risk Benefit Conundrums'.<sup>2</sup> This paper, which analysed US Food and Drug Administration (US FDA) licence applications in the late 1980s, revealed a doubling of suicide risk in subjects given antidepressants compared to placebos.

#### A KNOWN PROBLEM

Despite the fact that these catastrophic side-effects had been known to the FDA since the late 1980s, they had not been disclosed to patients or

prescribers. Further investigation revealed that PHARMAs had 'cherry-picked' the trials with the best results to present to licensing agencies.<sup>3</sup> Misinforming the FDA and the Therapeutic Goods Administration (TGA), its Australian equivalent, had been deliberate, systematic and widespread.

The efficacy of the drugs had also been wildly exaggerated. Some reported effects might have been due to co-prescribed medication (Valium), the use of which had also not been revealed.

Healy's paper sparked Congressional hearings in the US, which revealed the disparity between the knowledge held by PHaRMAs and the information that they disclose in their advertising. The FDA was ordered to issue a Public Health Advisory, published on 22 March 2004, some 15 years after this information should have been made public.

**Subject: WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS**

'Today the Food and Drug Administration (FDA) ... recommends close observation of adult and pediatric patients for worsening depression or the emergence of suicidality. The drugs that are the focus of this new Warning are: Prozac (fluoxetine); Zoloft (sertraline); [Aropax] (paroxetine); Luvox (fluvoxamine); [Cipramil] (citalopram); Lexapro (escitalopram); Zyban, (bupropion); Efexor (venlafaxine); Serzone (nefazodone); (now withdrawn) (and [Avanza] (mirtazapine).

- Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases. Although the FDA has not concluded that these drugs cause worsening depression or suicidality, health care providers should be aware that worsening of symptoms could be due to the underlying disease or might be a result of drug therapy.
- Health care providers should carefully evaluate patients in whom depression persistently worsens, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms, to determine what intervention, including discontinuing or modifying the current drug therapy, is indicated.
- Anxiety, agitation, panic attacks, insomnia, irritability, hostility,

impulsivity, akathisia (severe restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although the FDA has not concluded that these symptoms are a precursor to either worsening of depression or the emergence of suicidal impulses, there is concern that patients who experience one or more of these symptoms may be at increased risk for worsening depression or suicidality. Therefore, therapy should be evaluated, and medications may need to be discontinued, when symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

- If a decision is made to discontinue treatment, certain of these medications should be tapered rather than stopped abruptly (see labelling for individual drug products for details).
- Because antidepressants are believed to have the potential for inducing manic episodes in patients with bipolar disorder, there is a concern about using antidepressants alone in this population. Therefore, patients should be adequately screened to determine if they are at risk for bipolar disorder before initiating antidepressant treatment so that they can be appropriately monitored during treatment. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.
- Health care providers should instruct patients, their families and their caregivers to be alert for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality and worsening depression, and to report such symptoms immediately to their health care provider.'

PHaRMAs had 'cherry-picked' the trials with the best results to present to licensing agencies.

More alarming information emerged from David Healy's evaluation of the clinical trials presented to the FDA of new 'atypical' antipsychotics (Zyprexa), aripiprazole (Abilify), risperidone (Risperdal) or quetiapine (Seroquel). Because of their high cost (\$300+ a month as opposed to \$10 a month for haloperidol) they are limited to use for the special purpose (SP) of schizophrenia. (Section 103 (5) *National Health Act 1953* states, in part – A person shall not: (b) obtain a pharmaceutical benefit to which the person is not entitled. This section has a penalty for contravention of \$5,000 or imprisonment for two years (or both.) In practice, they are very frequently prescribed unlawfully (or 'off-label') for all sorts of problems, with the best of intentions. They are problematic drugs.

In the late 1980s, the FDA (and sponsors) did not reveal that 1 in 208, or 12 in 2,500, clinical trial subjects with schizophrenia committed suicide during the trials of Zyprexa, but only one on placebo and one on a comparator, most likely haloperidol. The overall suicide and death rate for these trials, on a time-adjusted basis, was two to five times the norm for schizophrenics. More than half the clinical trial subjects could not tolerate the drugs at all and did not complete six-week trials. None of the drop-out rates, suicides or deaths was revealed in any published information about these medicines.

A further US FDA Public Health Advisory was issued on 11 April 2005. >>

**Subject: DEATHS WITH ANTIPSYCHOTICS IN ELDERLY PATIENTS WITH BEHAVIOURAL DISTURBANCES**

'... Of a total of 17 placebo-controlled trials performed with olanzapine (Zyprexa), aripiprazole (Abilify), risperidone (Risperdal), or quetiapine (Seroquel) in elderly demented patients with behavioural disorders, 15 showed numerical increases in mortality in the drug-treated group compared to the placebo-treated patients. These studies enrolled a total of 5,106 patients, and several analyses have demonstrated an approximately 1.6-1.7-fold increase in mortality in these studies.'

The TGA has refused to pass on these FDA advisories: on 'New Generation Drugs'; on the risk of sudden death on selective serotonin reuptake inhibitors (SSRIs); and the near-doubling of sudden death on antipsychotics.

Both regulatory bodies have turned a blind eye to the existence of the large numbers of clinical trials that had been withheld by sponsors. Both ignored the massive medical literature on lethal and sub-lethal side-effects and court decisions about their causation in civil and criminal jurisdictions. Both appear to have been vulnerable to pressure from 'big' Pharma interests.

According to Professor Beverley Raphael (then Director of the NSW Mental Health Unit),<sup>4</sup> the number of persons needing hospitalised mental health care doubled in the decade to 2002. The NSW Department of Health had been unable (or unwilling) to make public its data. Violence in mental health patients, so visible in emergency departments, has increased, along with suicides. Suicides by patients under mental health care increased by several hundred per cent after 1991 (30-156 annually), and homicide, together with lesser attacks, increased from rare to nine cases in three years. These increases were documented in the report of the NSW Sentinel Events Committee, *Tracking Tragedy*, published in December 2003 by the NSW Department of Health, on its website.

The suicide rates in formerly withheld trials have now been reviewed and published.<sup>5</sup> On average, they show a doubling of risk of suicide attempts on active substance. This prompted a further FDA Advisory (30 June 2005) and further investigation, but the TGA ignored this as well.

### HISTORY

Prozac and her sisters were made available sequentially from 1991, and 'atypical antipsychotics' from 1995. A crisis in mental health was identified as presentations doubled in the following decade (1992-2002). The number of 'seriously mentally ill persons' increased again by 15% in the four years to 2005. The Department of Health has been informed many times of the cause of this, but does not seem to want to know about this problem, or to solve it. According to *The New York Times*,<sup>6</sup> psychiatrists and their institutions, worldwide, are in denial.

Psychiatrists stand to benefit from this 'boom': burgeoning patient numbers create a lever to attract even more taxpayers' money, over and above the \$500m already spent on antidepressants annually by the Commonwealth.

Every year in Australia, some 400 suicides and countless attempts (plus more bleeding and cardiac deaths) are likely to be caused by the combined use of antidepressants and 'atypical' antipsychotics, which are neurotoxic and cardiotoxic for some people.

Suicidality and 'hostility' (in practice, violence and homicide) in children and adolescents had been the subject of earlier FDA advisories in 2003 (and these have been posted by the Adverse Drug Reactions Advisory Council – ADRAC – for the TGA). A huge increase in the death rate in schizophrenic patients has followed in many countries and should be of concern in Australia. One in 20 people in Australia has been prescribed these drugs.<sup>7</sup>

The trial subjects used in SSRI testing came from 'the Valium-using population of the 1970s' with suicide-risk patients weeded out. On new antidepressants, this population had committed suicide at a rate of 2 in 1,000 or 1 in 500 (200/100,00 as

opposed to the population rate of 0-30/100,00 for persons suffering minor disorders), and 10 to 20 times that number had made suicide attempts. They had become manic at up to 20 times the expected rate, and violent.

These drugs were targeted at general practice where users get even less supervision than do clinical trial subjects. When a treated population is large, even very rare side-effects become common. These side-effects are proving to be a public health disaster, largely through akathisia.

The association of akathisia with suicide, violence behavioural dyscontrol and deterioration in mental condition, even substance-induced psychosis, is a matter of basic textbook psychiatry.<sup>8</sup> Behavioural toxicity and dyscontrol can be side-effects of psychiatric medications in some people. The finding of akathisia opens a defence of involuntary intoxication, which in psychiatry, if not in law, leads to dissociation and automatism.

The serious side-effects of SSRIs have been known for some time. The crisis in mental health is identified as beginning roughly when these drugs came on to the market. It is not drawing too long a bow to see a connection.

### PROPER DIAGNOSIS

All mental illnesses, schizophrenic and bipolar disorder have an exclusion clause in their diagnostic criteria:

Criterion E Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition.<sup>9</sup>

If these criteria are adhered to, the population rates of bipolar and schizophrenia are stable across cultures and have not changed for one hundred years. If they are not adhered to, the prevalence of 'serious mental illness' increases beyond rational expectations.

The excess cases of 'serious mental illness' are likely to be cases of chemically induced side-effects, which should be diagnosed as 'psycho-active substance-induced disorders'. These

can then be classified as 'with delusions, hallucinations, like schizophrenia, predominantly manic, depressive' and so on, according to the International Classification of Diseases (ICD 10), which is still Australia's official diagnostic system. They can be treated successfully by withdrawing the offending substances, and made worse by adding more.

Suicidal and violent acts on new generation antidepressants accounted for one-third of admissions to a rural psychiatric unit in 2003 and 2004.<sup>10</sup> Iatrogenic psychosis and mania accounted for at least 8% more, in other studies. Peter R Breggin documented this litany of side-effects,<sup>11</sup> describing both lethal and sub-lethal side-effects that require hospitalisation or attract criminal charges. Iatrogenic illness and the widespread prescribing of poorly tolerated and frequently ineffective drugs contribute to the crisis in mental health much more than under-funding. PHaRMAs reap huge profits and the taxpayer, who

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funds the health services, picks up the costs of side-effects.

Drug-induced illness should be diagnosed as such. That it often is not contributes to the evidence of a 'crisis in mental health'.

**SSRIs AND THE LAW**

All medicines, psychiatric or other, that list akathisia among their side-effects, have the potential to cause a deterioration in mental condition, exacerbating dysphoria in a variety of ways with increasing anxiety, depression, aggression, psychosis, delirium, confusion and impulses to suicide, violence and homicide. Some hundred homicides (and many more

attempts) have been defended worldwide as caused by akathisia, with outcomes dependent on local law and the nerve of the defence.

In the case of *Regina v Hawkins*,<sup>12</sup> a 70-year-old man with no prior psychiatric history became acutely akathisic on Zoloft, killing his wife and attempting suicide. O'Keefe J found that 'but for' the Zoloft, he would not have killed his wife.

The accused can plead a defence of involuntary intoxication and non-insane automatism and may get a 'not guilty' verdict. This defence also succeeds in lesser charges of violence, in lower courts and is frequently invoked in s33 reports under the

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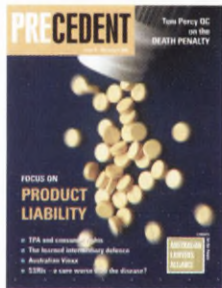
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*Mental Health (Criminal Procedure) Act 1990.*

In 2004, New York's Attorney General, Eliot Spitzer, won a settlement of US\$430m against Warner Lambert, a subsidiary of Pfizer Inc, for illegal and deceptive promotions of one of its blockbuster drugs, Neurontin (gabapentin). A score of US state attorneys have followed suit, expecting windfall income for state coffers to recoup some of the health care costs generated by the indiscriminate use of these drugs. "It is critically important that physicians and their patients receive fair, balanced and accurate information about prescription drugs and the conditions these medications are approved to treat," Spitzer said. "Marketing strategies that deceptively and illegally promote drugs for unapproved purposes in order to increase a pharmaceutical company's bottom line will be aggressively investigated."

Following further litigation against Glaxo SmithKline by Spitzer, the PHARMAs agreed to post all clinical trials on the FDA website. This has provided a resource enabling an expert to demonstrate the disjunction between information emerging from clinical trials, the *MIMS Annual*, which is the basic prescribing guide, and information in the Pharma promotional 'literature' with which psychiatrists and their institutions are bombarded (along with gifts, travel, research and conference funding).

## CONCLUSION

Merck defended its drug, Vioxx, against charges that it caused heart problems until two weeks before it was withdrawn. One week before it was withdrawn, and in the face of evidence that had been in the public arena for four years or more, the FDA approved the use of Vioxx for children. Similarly, suicides and sudden deaths in FDA trials did not appear in MIMS or sponsors' summaries in Australia.

Despite some 400 deaths in Australia currently being sheeted home to Vioxx, the scandal associated with psychiatric drugs has the potential to dwarf it. However, Vioxx is one of 20 similar cases where drugs have been withdrawn

for safety reasons. Little attention is paid in Australia to these matters.

The FDA claims that its role is to license drugs, not protect the public. The TGA has repeatedly been advised that that it cannot trust sponsors' summaries without doing its own research. It appears sanguine about litigation. ("The TGA gets sued all the time", officials tell me.) The TGA is not giving priority to protecting the public.

A high-level inquiry into the practice of psychiatry and its relationship to the pharmaceutical industry (and its fraudulent hypotheses) is long overdue.

- Notes:** **1** *William Daubert et ux, etc, et al Petitioners v Merrell Dow Pharmaceuticals Inc*, Supreme Court of the USA, 28 June 1993. **2** *Psychiatry Neuroscience* 2003; 28(5): 331-7. **3** The term 'PhARMA' comes from the initials of the Pharmaceutical Research and Manufacturers of America. **4** Cited in *The Bulletin*, 3 October 2003. **5** 'Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials', Fergusson et al, *BMJ* 2005, 330:396. **6** 6 December 2004. **7** <http://www.abc.net.au/cgi-bin/common/printfriendly.pl?http://www.abc.net.au/news/newsitem/s/200501/s1292466.htm> **8** *Diagnostic and Statistical Manual of Mental and Behavioural Disorders*, American Psychiatric Association (known as 'DSM 1V') 333.99, and all editions since its inception. **9** DSM 1V. **10** Lucire Yolande, 'New drugs, new problems', *Australian Journal of Forensic Sciences*, 37:1 9-25, 2005. **11** 'Suicidality, violence, and mania caused by selective serotonin reuptake inhibitors (SSRIs): A review and analysis', *International Journal of Risk & Safety in Medicine*, 16 (2003/2004) 31-49 [www.breggin.com/31-49.pdf](http://www.breggin.com/31-49.pdf) **12** [2001] NSWSC 420, SCNSW, *R v B* 67 of 2004 SCWA.

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