The Canadian Journal of Psychiatry

Volume 54 Ottawa, Canada, February 2009 Number 2

In Debate

Are Selective Serotonin Reuptake Inhibitors a Risk Factor for Adolescent Suicide?

David Healy, MD, FRCPsych[1]

Can J Psychiatry. 2009;54(2):69–71.

In 1959, at a meeting in Cambridge celebrating imipramine—a potent serotonin reuptake inhibitor—a series of speakers distinguished between the recognized risk of suicide stemming from electroconvulsive therapy rolling back psychomotor retardation before depressive suicidality was alleviated and imipramine-induced agitation and suicidality.[1] Thereafter, the received clinical wisdom in Europe was that antidepressants could trigger suicidality.

When SSRIs came on stream, controlled trials had become an important method of evaluating their clinical effects. Had these trials been meta-analyzed for suicidal acts, it is now clear that as of 1988 they would have shown a doubling of the risk of suicidal acts on SSRIs, compared with placebo.[2]

Against this background, a series of articles between 1990 and 1992 describing an early onset, dose-related emergence of suicidality on fluoxetine that cleared on discontinuation and reemerged on reexposure was not surprising.[3] Using all standard causality algorithms, these studies demonstrated a convincing causal link between treatment and adverse effect. The original article described 6 nonfatal cases but omitted a death by suicide in a person aged 14 years with obsessive–compulsive disorder.[4] King et al[5] described identical effects in children to those in adults.

While claiming that there was no significant difference in suicidal act rates between active treatment and placebo, all meta-analyses of clinical trial data from 1991 to 2005 in fact reported an excess of suicidal acts on active treatment.[6] The excess would have been greater but for the fact that these analyses included, under the heading of placebo, acts that happened during the pre- and (or) post-randomization phase of the trials analyzed.[6] A 2003 analysis of placebo-controlled trials of antidepressants in anxiety concluded—on the basis of 11 suicides in 12 914 patients on active treatment, compared with 0 suicides in 3875 patients on placebo—that anxiety was a risk factor for suicide, suggesting a profound bias against recognizing the risks stemming from treatment.[7]

In 2004, the suicide risk of antidepressants came to the fore as linked to possible inefficacy of these agents in children, providing evidence for widespread failure to report trials and ghostwriting of those published. FDA analyses of the data confirmed a doubling of the risk of suicidal behaviours on active treatment, compared with placebo.

Among those concerned that these data may deter patients from seeking treatment, it has been claimed that: there were in fact no deaths by suicide in these trials, increased risk may stem from patients on active agents verbalizing their ideation or acts, and, since the launch of SSRIs, national suicide rates have largely fallen. A series of articles have shown suicidal act rates falling in depressed patients after the institution of treatment, and there have been suggestions of increased pediatric suicide rates in the United States and Holland since warnings were placed on antidepressants, although these uncontrolled studies may demonstrate little more than the fact that patients with any condition, from influenza to depression, seek or receive treatment when at their worst, and the natural history of these disorders leads to an improvement in the post-consultation period, even if no effective treatments are available.

The argument from national suicide rates omits data from the 1960s and 1970s when national suicide rates climbed, even

Table 1 Suicides and suicidal acts in adult placebo-controlled trials of antidepressants

	Active drug		Placebo		Active drug		Placebo	
Antidepressants	Subjects	Suicides	Subjects	Suicides	Subjects	Suicidal acts	Subjects	Suicidal acts
Citalopram[a]	1320	1	0622	1	1320	11	0622	5
Escitalopram[a]	2648	0	2088	1	2648	6	2088	5
Fluvoxamine[a]	4186	2	3396	2	4186	24	3396	10
Mirtazapine[a]	2618	5	0388	0	2349	9	0388	3
Sertraline[a]	7169	4	5108	0	7169	20	5108	8
Venlafaxine[a]	6153	4	2962	0	6153	25	2962	8
Paroxetine[b]	8172	1	5391	0	8172	16	5931	4
Total	32 267	17	19 955	4	32 267	118	19 955	30

[a] Data from the Expert Working Group on the Safety of Selective Serotonin Reuptake Antidepressants 2004.[11]

[b] Data from adult depression trials (minus intermittent brief depression).[12]

Table 2 Suicides in adult placebo-controlled trials of antidepressants from FDA review[a]

	All antidepressants		Placebo	
Subjects' age, years	Subjects	Suicides	Subjects	Suicides
18 to 24	5128	5	2831	0
25 to 64	53 133	6	29 854	2
Total	58 261	11	32 685	2

[a] Table based on data from Stone and Jones.[13]

though antidepressant prescriptions among those at greatest suicide risk increased maximally. The 1990s' data fail to distinguish between the 80% of antidepressants administered in longer-term treatment to patients at little risk from their treatment, and the at-risk group of first-exposure patients who take possibly no more than 20% of antidepressant prescriptions in any 1 year. Once such distinctions are made, it is possible to reconcile an increased exposure to a treatment-induced risk with falling national suicide rates.[8]

Further, there is clear evidence that during the period when both national suicide rates and antidepressant prescriptions rose, autopsy rates also rose, while the recent fall in suicide rates coincides with falling autopsy rates, and increased rates of deaths from unspecified causes.[9]

Factors such as these need to be taken into account if we are to avoid a 1960s' scenario when tobacco companies denied there was a link between smoking and either lung cancer or cardiac disorders on the basis of 60 years' worth of national data showing falling deaths from respiratory and cardiac causes and increased life expectancy coincident with increased cigarette consumption.[10]

RCTs offer some protection against the risks of confounding inherent in data from large uncontrolled cohorts. No antidepressant RCTs have been designed to look at treatment-induced suicidality. Given this, deaths by suicide offer the least ambiguous outcome, suicidal acts a less certain outcome, and suicidal ideation a more ambiguous outcome. The data from the review of suicidal behaviours posted by the British regulator in 2004 shows a 2.62-fold increase in completed suicides (95% CI 0.89 to 7.81) and a 2.4-fold (95% CI 1.63 to 3.63) increased relative risk in suicides and suicidal acts combined on active agents, compared with placebo (Table 1).

Data from FDA's recent review of adult trials (Table 2) shows a 3.09-fold (95% CI 0.68 to 13.9) increased relative risk of death by suicide in people aged 18 to 64 years, compared with placebo. There was a 2.3-fold increased rate of suicidal behaviours in people aged 18 to 24 years, a 0.9-fold relative risk of suicidal behaviours in people aged 25 to 44 years, and a 1.75 relative risk of suicidal behaviours in people aged 45 to 64 years, compared with placebo. There was an overall increase in the risk of suicidal behaviours for people

Abbreviations used in this article

FDA	Food and Drug Administration
RCT	randomized controlled trial
SSRI	selective serotonin reuptake inhibitor

aged 18 to 64 years, but a reduced risk compared with the suicide risk.

There are discrepancies between the data reported by British and American regulators and other data in the public domain. There may be numerous reasons for continuing disparities. One reason lies in an inappropriate inclusion in certain analyses of data from 2 paroxetine trials, 057 and 106, in which 298 patients, primarily in the group aged 25 to 44 years, had 77 suicidal acts. For instance, including these data in Table 1 would reduce the relative risk of suicidal acts from 2.43 to 1.43.

It is worth noting that, in response to the claim that there were no suicides in pediatric trials of antidepressants, it is more accurate to state that no suicides have been recorded. A large number of patients in these trials dropped out because of adverse events and were lost to follow-up. Given the rate of suicides in the FDA data for people aged 18 to 24 years (which does not include all adolescent deaths by suicides from placebo-controlled trials), it would be imprudent to discard the possibility that there were in fact suicides in the pediatric trials. It is also worth noting that the data on suicides and suicidal acts contrasts with the data on suicidal ideation and suggests there was no reporting bias.

What Can Be Learnt From This?

First, antidepressants pose a risk of suicide in all age groups. Second, after 100 000 patients have been entered into placebo-controlled trials, and more than a 1000 company trials of antidepressants, it seems extraordinary that clinicians cannot match specific pharmacotherapies to their patients. There is still a 50–50 chance that the next patient prescribed one of these drugs, from whatever age group, will be prescribed the wrong drug for them. The science of therapeutics has not moved forward one inch. Third, psychiatrists need to revisit the issue of when to believe and when not to believe the evidence before their own eyes. The original case reports were broadly correct but their truth might easily have been hidden. Had antidepressants prevented more suicides than they appear to have triggered in these patient groups, clinicians faced with patients exhibiting *de novo* suicidality might have had no data to bolster their arguments.

In contrast, the data from controlled trials indicate that clinicians treating both adults and children appear to overestimate the benefits of treatment, claiming the treatments work when 80% of the response is reproduced by placebo.

The data now available call for a judicious skepticism regarding the benefits of treatment and a real concern about hazards. The concealing of data raises ethical and scientific concerns about company sequestration of data and the ghostwriting of trial data.

Funding and Support

No funding was provided for this research.

Dr Healy has consulted with, and been a principal investigator, a clinical trial list, a chairman, or a speaker at international symposia for, Astra-Zeneca and Servier. He received support to attend meetings from Astra-Zeneca and Servier, and received lecture fees and support to attend meetings from Astra-Zeneca.

Dr Healy has received compensation as an expert witness for the plaintiff in 15 legal actions involving SSRIs and has been consulted on numerous 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 also been an expert witness in one patent and one securities case.

References

1. Clark D, Kristiansen E, Jensen E, et al. In: Beresford Davies E, editor. Depression: proceedings of the symposium; 1959 Sep 19–22; Cambridge, GB. Cambridge (GB): Cambridge University Press; 1964. p 86–89.
2. Fergusson D, Doucette S, Cranley-Glass K, et al. The association between suicide attempts and SSRIs: a systematic review of 677 randomized controlled trials representing 85,470 participants. BMJ. 2005;330:396–399.
3. Healy D. Let them eat prozac. New York (NY): New York University Press; 2004.
4. Teicher MH, Glod C, Cole JO. Suicidal preoccupation during fluoxetine treatment. Am J Psychiatry. 1990;147:1380–1381.
5. King A, Riddle MA, Chappell PB, et al. Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. J Am Acad Child Adol Psychiatry. 1991;30:171–176.
6. Healy D. Did regulators fail over selective serotonin reuptake inhibitors. BMJ. 2006;333:92–95.
7. Healy D. The antidepressant tale: figures signifying nothing? Adv Psychiatr Treat. 2006;12:320–328.
8. Healy D, Aldred G. Antidepressant drug use and the risk of suicide. Int Rev Psychiatry. 2005;17:163–172.
9. Reseland S, Le Noury J, Aldred G, et al. Contributions to national suicide rates: autopsies and antidepressants. Psychother Psychosom. 2008;77:78–82.
10. The Tobacco Institute, Inc. Tobacco and the Health of the Nation. In: The Legacy of Tobacco Documents Library [Internet]. San Francisco (CA): University of California; 1969 [cited 1994 Dec 10]. Available from: http://legacy.library.ucsf.edu/cgi/getdoc?tid=dxb34f00&fmt=pdf&ref=results.
11. Expert Working Group on the Safety of Selective Serotonin Reuptake Antidepressants 2004. Safety of antidepressants [Internet]. London (GB): Medical and Healthcare Products Regulatory Agency; 2004 [cited 2006 May 13]. Available from: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=1391&noSaveAs=1&Rendition=WEB.
12. GlaxoSmithKline. Paroxetine adult suidality analysis [Internet]. GlaxoSmithKline; 2006 [updated 2006 Apr 5; cited 2007 Aug 8]. Available from: http://www.gsk.com/media/paroxetine/briefing_doc.pdf.
13. Stone M, Jones L. Clinical review: relationship between antidepressant drugs and adult suicidality [Internet]. Washington (DC): United States Food and Drug Administration; 2006 [cited 2006 Dec 10]. Table 16, p 26; Table 18, p 30. Available from: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006–4272b1-index.htm.

Manuscript received May 2008 and accepted July 2008.

[1]Professor of Psychiatry, North Wales Department of Psychological Medicine, Cardiff University, Hergest Unit, Ysbyty Gwynedd, Bangor, Wales.

Address for correspondence: Dr D Healy, North Wales Department of Psychological Medicine, Cardiff University, Hergest Unit, Ysbyty Gwynedd, Bangor, Wales, LL57 2PW United Kingdom; David.Healy@nww-tr.wales.nhs.uk; Healy_Hergest@compuserve.com