

## The Risk of Suicidality with Selective Serotonin Reuptake Inhibitors

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### Abstract

**Antidepressants are efficacious in the treatment of depression but they are not without side effects. The recent findings on the risk of suicide with selective serotonin reuptake inhibitor treatment, however, have raised serious concerns about the risk-benefit ratio of their use. The development of the concerns is traced and the risks discussed, particularly in the child and adolescent group. The prescriber needs to be aware of the issues and of the need for close clinical monitoring of patients started on selective serotonin reuptake inhibitor treatment.**

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**Key words:** Antidepressants, Self-injurious behaviour, Suicide attempt

### Introduction

The first antidepressants were discovered 50 years ago by chance. Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) dominated the treatment of depression from the late 1950s until the late 1980s, when selective serotonin reuptake inhibitors (SSRIs) were introduced. Antidepressants are efficacious but there have been various safety concerns over the years.

The recent concerns relate to the risk of suicide with antidepressant use. Depression is a mood disorder. In addition to the biological symptoms of depression, suicidality is also a symptom (Table 1). The possibility of a suicide attempt is inherent in major depressive disorders, and the risk may persist for awhile, until significant remission occurs.

As part of the assessment and management, all depressed patients should be carefully monitored, especially in the initial phases of treatment. Antidepressants sometimes provide activation, giving patients the motivation and energy to act on suicidal thoughts and/or impulses. Slater and Roth's *Clinical Psychiatry*,<sup>1</sup> published more than 40 years ago, and a standard textbook for many years refers to observations in patients during initial treatment with TCAs: "with beginning convalescence (following initiation of treatment with tricyclic antidepressants), the risk of suicide once more becomes serious as retardation fades". The term

Table 1. Diagnostic Criteria for Major Depressive Disorder\*

1. depressed mood most of the day, nearly every day
2. markedly diminished interest or pleasure
3. significant weight loss when not dieting or weight gain
4. insomnia or hypersomnia nearly every day
5. psychomotor agitation or retardation
6. fatigue or loss of energy nearly every day
7. feelings of worthlessness or excessive or inappropriate guilt
8. diminished ability to think or concentrate or indecisiveness
9. recurrent thoughts of death, recurrent suicidal ideation or a suicide attempt or a specific plan for committing suicide.

\* from DSM-IV<sup>TM</sup>, American Psychiatric Association

"roll-back phenomenon" is used to describe this presentation.

### Initial Findings

While there were occasional reports of antidepressant-induced suicidality in the 1970s and 1980s, the concerns intensified in 1990 with an article published in the *American Journal of Psychiatry*.<sup>2,3</sup> Teicher, a psychiatrist at Harvard Medical School, and his colleagues reported on 6 depressed patients who, in their view, had become suicidal as a result of treatment with fluoxetine, a SSRI. These patients had never experienced suicidal ideation but had developed "persistent, obsessive and violent suicidal thoughts" after a period of treatment with fluoxetine. Their periods of

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treatment had ranged from 2 weeks to 7 weeks. In 1 patient, the symptom resurfaced when fluoxetine was reintroduced. The suicidal thoughts abated in most patients in an average of 87 days (range, 60 to 106) after fluoxetine was stopped.

This was followed by further reports, leading Lilly, the manufacturer, to reanalyse their clinical trial data for the emergence of suicidality. The US Food and Drug Administration (FDA) also re-evaluated its spontaneous reports database to check whether there was any signal of increased risk.

A year later in September 1991, this issue was brought up at a Psychopharmacological Drugs Advisory Committee (PDAC) Meeting at the FDA Center for Drug Evaluation and Research.<sup>4</sup> While the FDA had found an increase in spontaneous reports of suicidality with fluoxetine, they related this to the Teicher report and the ensuing publicity. The National Institute of Mental Health (NIMH) was not convinced the data supported an increase in suicidality with antidepressants and Lilly's analysis of the data from their various clinical trials also did not reveal any increased risk to patients.

At that meeting, Dr Teicher proposed various mechanisms to explain the possible increase in suicidality. The first was the "roll-back phenomenon" described earlier. Another possibility was a paradoxical worsening of depression despite treatment with antidepressants. A third possible cause was akathisia or an inner restlessness commonly associated with antipsychotic use but which sometimes occurs with antidepressant use. Some antidepressants could also induce anxiety and panic attacks, increasing the risk of suicidality. So too insomnia and finally "stage shifts", when patients become hypomanic/manic with antidepressant treatment because of an underlying, unrecognised bipolar disorder.

### Subsequent Developments

Over the next decade, other case reports and studies surfaced. Data for suicide risk with antidepressant use come from various sources. There are data from clinical trials which do not show a higher risk of suicide with antidepressant use. In fact, one study showed that the risk of suicide also existed with antipsychotic and anxiolytic use.<sup>5</sup> Therefore, there was no consistent relationship between suicide behaviour and any pharmacological class of drug or even dose response. FDA analyses of adult data on completed or attempted suicides revealed that the risk of completed suicide was the same whether the patient was on an antidepressant or a placebo.<sup>6</sup> Analyses of completed suicides in 234 randomised controlled trials involving 20 antidepressants for major depression also showed no increased risk for adults, whether they were prescribed an antidepressant or a placebo.<sup>7</sup>

Clinical trials in children, however, reported results differently. Suicidal behaviour was captured in adverse event reports. As with adult studies, trials in children did not set out specifically to determine whether antidepressants led to suicide. Therefore, reporting and defining suicidal behaviour is different, making comparisons across trials and even within trials almost impossible. Despite this, it is significant that in all the trials involving more than 2000 children, not a single patient committed suicide.

Data on suicide risk with antidepressant use also come from epidemiological studies. These in general seem to support a decrease in suicide rates, averaging about 33% across 15 countries over a period of 14 years. This decline coincides strikingly with significant increases in antidepressant prescriptions, particularly SSRIs, to adolescents, suggesting a causal relationship.<sup>8</sup> Another analysis of prescription data from the largest pharmacy benefit service organisation in the United States (Advance PCS, Irving, Texas), the national suicide mortality files and regional socio-demographic data from the 1990 and 2000 US census, showed that a 1% increase in adolescent use of antidepressants was associated with a decrease of 0.23 suicides per 100,000 adolescents per year.<sup>9</sup>

The third repository of data for suicide risk with antidepressant use is autopsy studies. If antidepressants had triggered suicides, toxicological analyses of those who had completed suicide would indicate higher levels of antidepressants. But the findings show the reverse – suicide is more likely when depressed patients do not take their medication rather than if they take an overdose. An open cohort study of 172,598 people who had at least 1 prescription for 1 of 10 antidepressants revealed that overdose with antidepressants accounted for only 14% of suicides.<sup>10</sup> Data from the National Institute of Mental Health Collaborative Depression Study, a prospective, naturalistic follow-up of 643 patients, of whom nearly 30% (n = 185) were treated with fluoxetine, did not support an increased risk of suicide. Leon et al<sup>11</sup> concluded that there was a non-significant reduction in suicide risk in patients treated with fluoxetine despite their being more severely ill at the start.

### Triggering Event

In 2003, a FDA clinical reviewer, in reviewing paroxetine data submitted to the FDA, found that events that could suggest possible suicidality were reported as "emotional lability". This led the FDA to ask the manufacturer GlaxoSmithKline (GSK) to "separate out ... the verbatim terms suggestive of suicidality".<sup>4</sup> While GSK's review findings suggested a higher risk of "possibly suicide related" events and "suicide attempts", this was clearest for "possibly suicide related" events in only 1 of 3 trials with paroxetine involving depressed children.

### Actions Taken by Regulatory Authorities

This resulted in the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issuing a public statement that paroxetine should not be used to treat depression in children and adolescents under the age of 18, and a labelling change contraindicating paroxetine in paediatric major depressive disorders.<sup>12</sup>

The FDA followed with similar advice but did not take labelling action. They did, however, request for data for 8 other antidepressants from placebo-controlled paediatric studies. These involved fluoxetine, sertraline, fluvoxamine, citalopram, bupropion, venlafaxine, nefazodone and mirtazapine.<sup>4</sup> The FDA's own review of clinical data from paediatric studies found inconsistent signals of increased suicide risk but the signals were mainly from studies for major depressive disorders. On their own accord, Wyeth, the manufacturer of Effexor (venlafaxine), made labelling changes to clarify that the medication is not recommended for children and also sent out a Dear Healthcare Professional Letter (DHPL) in August 2003.

In September 2003, the MHRA, UK advised against treating depressed children with venlafaxine, and in December 2003, advised against using all SSRIs, except fluoxetine, in children. An FDA advisory was issued in October 2003, indicating that preliminary data suggested an increased risk of suicidality but that further research was needed. However, by March 2004, the FDA had issued a Public Health Advisory cautioning physicians, patients, families and caregivers on the need for dose monitoring of depressed children and adults, particularly at the beginning of treatment or when doses are adjusted.<sup>12</sup>

By October 2004, the FDA had completed a review of 24 trials involving more than 4400 children and adolescents with major depressive disorders, obsessive compulsive disorder, and other psychiatric disorders. There was a greater risk of suicidality in the first few months of treatment and the average risk of 4% was twice the placebo risk of 2%. However, it is important to note that there were no suicides in any of these trials. The FDA called for a black box warning on antidepressant use in children and adolescents.<sup>13</sup> Manufacturers of all antidepressants had to warn prescribers of an increased risk of suicidality in this age group.

### Recent Studies

As the debate continued, various researchers undertook further analyses. Fergusson et al<sup>14</sup> reviewed 87,650 patients from 702 randomised controlled trials (Medline and Cochrane Collaborations Register of Controlled Trials, November 2004) comparing a SSRI with either a placebo or an active non-SSRI control. They documented a

significant increase in the odds of suicide attempts for patients receiving SSRIs compared with the placebo (odds ratio 2.28, 98% confidence interval 1.14 to 4.55). However, there was no increase in fatal suicide attempts for those on SSRIs compared to those on placebo and no difference between those on SSRIs and on TCAs.

Gunnell et al<sup>15</sup> reviewed published and unpublished randomised controlled trials submitted by pharmaceutical companies to the MHRA; this involved 40,000 patients in 477 randomised controlled trials. There was no evidence of an increased suicide risk, and only weak evidence of an increased risk of self-harm.

A study of the General Practice Research database in the UK involving 146,095 patients treated with an antidepressant found no evidence of increased suicide or self-harm risk in adults on SSRIs.<sup>16</sup> There was, however, some weak evidence of an increased risk of non-fatal self-harm among those aged 18 years and below. The authors were unable to rule out confounding factors, such as a higher risk of suicide behaviour amongst these patients before the commencement of treatment with SSRIs.

### The Situation in Singapore

The Health Sciences Authority has a position statement on the use of SSRIs and related antidepressants in children and adolescents.<sup>17</sup> It has also advised local practitioners on the risks involved.<sup>18</sup> In Singapore, only fluoxetine is licensed for treating major depressive disorders in children and adolescents.

The local stand is similar to that of the US FDA, advising caution on the increased risk of suicidal ideation and behaviour in the young. The risk-benefit ratio in adult patients treated with antidepressants is still accepted as favourable.

### Conclusion

The issue of SSRIs and suicidality encompasses larger ethical dilemmas, such as the rigorousness of clinical trials, publication bias in favour of positive trials and even the complex issue of evaluating risk of harm.<sup>19,20</sup> The media has also been blamed for fuelling the concerns about SSRIs and suicide risk.<sup>21</sup>

While we are clear on the risk benefit in depressed adults treated with antidepressants, caution is definitely needed in the management of depressed children and adolescents at this point. Research data for the efficacy of SSRIs in this age group is poor. Published and unpublished data indicate that the risks could outweigh the benefits of these drugs, with the exception of fluoxetine, in children and adolescents.<sup>22</sup> The available data are also not reliable on the risk/benefits of SSRI or, for that matter, the use of any type

of antidepressant in patients with varying degrees of depression and with/without risk of suicide at the onset of treatment.

More analyses of available data are needed. What constitutes the risk is still open to discussion. The clinician on the ground, however, has to be guided by good clinical practice in daily management. This is where the advice to “begin antidepressant treatment carefully, monitor patients closely and watch for signs of untoward side effects, worsening symptoms and increased suicidality” cannot be repeated often enough.<sup>11</sup>

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