

Suicidality with selective serotonin reuptake inhibitors: Valid claim?

Yvon D. Lapierre, MD

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The red flags raised by the 1990 clinical reports of increased suicidality associated with treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine were followed by anecdotal reports of similar symptoms with other antidepressants of the same class. Recent discussions by Healy have argued in favour of a suicidogenic potential of the SSRIs. This paper reviews the relevant literature addressing the epidemiological data of Western populations and the data accumulated from clinical trial databases in several countries. The evidence currently available does not support the hypothesis that antidepressants or, more specifically, SSRIs cause increased suicidality in patients with depression, nor do they appear to do so in patients treated with these drugs for other reasons.

Les signaux d'alarme auxquels ont donné lieu les rapports cliniques de 1990 portant sur une augmentation des tendances suicidaires liée à l'administration d'un traitement à la fluoxétine, inhibiteur spécifique du recaptage de la sérotonine (ISRS), ont été suivis par des rapports isolés de symptômes semblables suite à l'administration d'autres antidépresseurs de la même catégorie. Les analyses récentes de Healy ont soutenu le potentiel suicidogène des ISRS. Cette communication passe en revue les écrits pertinents portant sur les données épidémiologiques s'attachant aux populations de l'Occident et sur les données accumulées dans les bases de données d'études cliniques de divers pays. À l'heure actuelle, les preuves disponibles n'appuient pas les hypothèses voulant que les antidépresseurs (ou plus particulièrement les ISRS) entraînent une augmentation des tendances suicidaires chez les patients atteints de dépression ou qu'ils aient cet effet chez les patients qui reçoivent ces médicaments pour d'autres raisons.

Introduction

A plethora of new antidepressants followed the introduction of the selective serotonin reuptake inhibitors (SSRIs) with the associated claims of their relative innocuity compared with the previous generation of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors. These claims seem to have reached

their high point, and SSRIs as well as other antidepressants are now undergoing a second phase of critical review. This reappraisal of antidepressants addresses not only the claims of efficacy but also those related to side effects and to the toxicological profiles of the old as well as of the newer products. These have challenged long-held views and have brought to light new findings that would most likely

Correspondence to: Dr. Yvon D. Lapierre, 401-1408 Riverside Dr., Ottawa ON K1G 5H2; lapierreyd@aol.com

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not have come about otherwise. Invariably, in such circumstances, the pendular shift of attitudes can easily lead to exaggerated claims toward the negative and unwanted effects to the point of discarding previously demonstrated positive findings. It is then necessary to have a critical and balanced expression of opinions and analytic reviews of the available data to arrive at a just appraisal of reality.

The risk of suicide has remained at around 15% in patients with mental disorders, with only a marginal decline of suicide rate since the advent of antidepressants. Over 50% of those who commit suicide have an associated mood disorder, which is usually depression.^{1,2} Long-term follow-up shows that this is more pronounced in unipolar depressives and that treatment lessens the risk somewhat, but it still remains above the norm.³

One considerably controversial issue has been the risk of suicide in relation to SSRI antidepressants. The issue arose from a series of case reports of patients who developed intense suicidal preoccupations and intense thoughts of self-harm while taking antidepressants. The initial reports implicated fluoxetine,^{4,5} and this was followed by reports suggesting a similar phenomenon with other SSRIs, thus leading to the speculation of a class effect.⁶

Retrospective analyses of some randomized controlled trials (RCTs) on SSRIs suggest that the incidence of suicide may be higher in patients undergoing treatment with this new class of antidepressant, but any conclusion is still uncertain.⁷⁻¹⁰ This leads to the purpose of this duo of papers (Healy and Whitaker¹¹ and this one), where facts may be submitted to different views and interpretation. Healy and Whitaker's contention is that SSRIs are conducive to an increased risk of suicide; this author disagrees.

The first question that arises is whether there is a temporal cause-effect relation between the administration of a specific drug and the development of suicidal ideation and of suicide. The order of such a cause and effect relation may then be examined and attributed, if applicable, as either a primary drug effect, a paradoxical drug effect, an expected side effect of the drug or, finally, an action that may be secondary to a side effect of the compound. A second issue to be addressed is whether this effect is drug specific or class specific. The question of validity of any imputed causality must be critically re-evaluated throughout this process. Once these issues are clarified, strategies that would improve

the outcome of treatment for patients with depression may arise.

This paper will address the problem by first looking at issues of efficacy and suicide data and then discussing the case for the alleged link between suicide and SSRI and other antidepressant therapies.

Efficacy issues

The efficacy of a widely used intervention may be evaluated by assessing its impact on the population at large through epidemiological approaches and then on the experiences obtained from clinical trials and clinical practice.

Epidemiological observations suggest that there has been a gradual increase in the incidence of depression in post-World War II generations. There are indications that this illness will become an ever-increasing burden of disability in Western societies.¹² Given that depression is the predominant risk factor for suicide, one would expect that with the increased numbers of depressed individuals, there would be an increase in suicide rates. Furthermore, if there is validity to the claim that SSRIs play a causative role in suicide, there would be an even greater increase in suicide rates since the advent of these drugs. Although this may not have materialized as such, these speculations are not necessarily dismissed as being completely invalid.

Epidemiological studies on the issue of antidepressant treatment and suicide have been conducted in a number of countries. In Italy, there was found to be a possible relation between increased SSRI use from 1988 to 1996 and suicide rate. There was a slight increase in suicide rates for men but a more pronounced decrease for women; however, these changes were not significant.¹³ In Sweden, from 1976 to 1996, increased utilization of antidepressants paralleled a decrease in suicide rates.¹⁴ In Finland, the increased use of SSRIs coincided with a decrease in suicide mortality, as well as with an increase in the incidence of fatal overdoses with TCAs. The tricyclics accounted for 82% of suicides by antidepressant overdose.¹⁵

In the National Institute of Mental Health Collaborative Depression Study, Leon et al¹⁶ assessed the possibility of an increased suicidal risk associated with the SSRI fluoxetine. In the 185 patients in follow-up, there was a trend for a decrease in the number of suicide attempts compared with patients receiving other treatments. Although this cohort was at higher risk because

of a history of repeated suicide attempts, treatment with fluoxetine resulted in a nonsignificant reduction of attempts in these patients.

The findings of these epidemiological studies do not provide any indication that the use of antidepressants, and more specifically SSRIs, contribute to an increased risk of suicide in population bases or in depressed populations.

The main sources of information on psychopharmacological agents are the data from clinical trials. Then, post-marketing studies are intended to provide the alerts on safety and potentially new indications for the drug. Both of these sources have limitations and biases, however, inevitably adding fuel to the present debate.

Given that RCTs are designed to primarily identify clinical efficacy and acute or short-term safety of antidepressants, there are limitations on the gathering of exhaustive data on unwanted side effects. The selection of patients for an RCT generally excludes those who are considered to be at risk for suicide. This is usually determined clinically, and the judgment is based on clinical indicators that have, in past experience, been associated with increased risk. Up to 80% of depressed patients may experience thoughts of suicide, and there is a greater than 15% risk of suicide with depression, making the elucidation of suicidal thoughts and intent increasingly relevant to a valid assessment of risk.

This rationale is based on the premise that suicidal ideation is the precursor to and is likely to lead to suicidal acting out. Suicidal acts in the recent past, as well as a number of other associated factors, contribute to the evaluation of risk and the decision of inclusion or exclusion. This inevitably leads to a skewed population, where those appearing to be most clearly at risk and those more severely depressed are often excluded.⁷

The experimental design most often used is a single-blind placebo-washout phase followed by a double-blind randomized phase with a placebo control, a standard active treatment control and an experimental treatment arm. Because of the pressures against the use of placebo in RCTs, as well as cost considerations, there is a trend toward having unbalanced groups, with fewer subjects in the placebo and control arms. This results in reduced statistical power and the need for more patients in the studies and has contributed to increasing numbers of multicentre trials to meet these and other exigencies.

The end point of an RCT is time limited, and the criteria of successful outcome are based on clinical evalu-

ations that of necessity are quantified using rating scales and focus on the immediate objective. They then have limited retrospective applicability and intrinsic limitations when explored retroactively for other purposes. This does not necessarily invalidate subsequent retrospective studies, but one must consider that there are limits on conclusions that can be reached because of these limitations and other biases. To mention but a few that may be relevant to the issue at hand, patient selection, diagnostic considerations and statistical limitations come to mind.

A similar pattern of biases occurs in post-marketing surveillance studies. The source of data varies from one jurisdiction to the next, as do the methods and obligations to report adverse events. Clinicians are known to adopt different prescribing patterns for patients presenting more severe states of depression and for those considered to be at greater risk for suicide. The former group are more likely to receive a TCA, whereas the latter are more likely to receive a "safer-in-overdose" SSRI. Thus, a significant bias in patient selection arises in the evaluation of suicidal risk under one form of treatment or another.¹⁷

Suicidality and suicide should be distinguished. Thoughts of suicide are not uncommon in the general population but become problematic if they are too frequent, intense or commanding and lead to greater risk of acting on the ideation. Most suicides are preceded by increases in suicidal ideation. Thus, this becomes an important consideration in the assessment of suicide risk. On the other hand, suicidal ideation as such cannot be totally equated to suicidal behaviour.¹⁸

Conditions favourable to acting on the ideation, such as increased impulsivity or a high level of anxiety and agitation, increase the risk of suicide. The suicidal tendencies item of the Hamilton Rating Scale for Depression is the instrument for quantification of suicidality in RCTs.¹⁹ It allows for a certain degree of quantification on the seriousness of suicidal tendencies and emphasizes mainly suicidal ideation as such. It is not meant to clearly discriminate and quantify the nuances of suicidality to allow for definitive conclusions to be drawn on the severity of the suicidal risk. However, it is probably the most widely used rating scale for RCTs on depression and has become the standard instrument for the analysis of the many features of this illness and for assessing change at different intervals during a clinical trial.

Meta-analyses of RCTs have yielded conflicting

results. The short duration of RCTs, which are the basis of these meta-analyses, may not provide valid long-term data, but they do contribute to an understanding of acute therapeutic effects. There is an inherent deficiency in meta-analyses because of the intrinsic limitations of post hoc analyses. Nevertheless, a few of these reports suggested that fluoxetine was associated with a greater incidence of suicidal thoughts. This was followed by other reports suggesting that sertraline, fluvoxamine, paroxetine and citalopram produced similar effects.^{4-6,20} This led to the speculation of a class effect of SSRIs. On the other hand, there are meta-analytic and other types of studies that just as strongly suggest that emergent suicidal ideation was lessened by these same SSRIs.^{21,22} In the Verkes et al study,²¹ the findings are more convincing because of the high-risk population involved. Others have suggested that, not only do SSRIs reduce suicidal ideation, but the symptom is increased in patients taking norepinephrine reuptake inhibitors.²³

A meta-analytic study of treatment with fluoxetine, tricyclic antidepressants and placebo in large samples of patients with mood disorders ($n = 5655$) and non-mood disorders ($n = 4959$) did not identify statistically significant differences in emergent suicidal thoughts between groups, and there were no suicides in the non-mood disorder group.²⁴ These data do not support a suicidogenic effect of SSRIs or TCAs.

Firm conclusions on suicidality and SSRIs based on these findings should be guarded at this point. Suffice it to say that the evidence to suggest that SSRIs generally reduce suicidality is more convincing than that supporting the contrary.

Suicide

The risk of a depressed patient committing suicide with prescribed antidepressants has been a long-standing concern of clinicians treating depressed patients. This was particularly significant with the older generation tricyclics^{25,26} and was one reason to advocate the use of the newer agents (because of their reported lower lethal potential in overdose). On the other hand, it is surprisingly rare for patients to use prescribed antidepressants for suicidal purposes. Data on the agents used for suicide from a number of countries suggest that only about 5% of overdoses are with antidepressants (range 1%–8%). An outlier appears to be the United Kingdom, with reports of 14%.¹⁸ Men commit suicide by overdose

much less frequently than women. An important finding in these reports is that patients tend to use previously prescribed undiscarded antidepressants as their drug of choice. This points to the important role of therapeutic failure in a number of patients who commit suicide.

The advent of the SSRIs brought a renewed impetus in physician and public education on depressive disorders to not only raise professional and public awareness of depression but also publicize the profile of the new antidepressants in their treatment. This, in addition to other factors, has led to many of these educational activities being sponsored by the pharmaceutical industry, with the inevitable ensuing risk of bias. These efforts have certainly contributed to a heightened awareness of depression by professionals and to less reluctance in using antidepressants because of improved safety profiles with equivalent efficacy.

Although antidepressants have been pivotal in the treatment of depression for more than 4 decades, a number of unanswered questions remain. The therapeutic superiority of antidepressants has been taken for granted despite the inconsistent robustness in many controlled studies, where their superiority over placebo is not always clearly demonstrated. Recent data on the latest generation of antidepressants, the SSRIs and serotonin–norepinephrine reuptake inhibitors suggest that only 48% of placebo-controlled studies show a consistent statistically significant superiority of the antidepressant over placebo.⁸ This figure may be inferior to the generally accepted greater success rate and emphasizes the need for individualized therapeutic strategies. This becomes critical for poor responders, where the limitations of available treatments become obvious. Depression is the main risk factor for suicide, the final and fatal outcome of non-response to treatment. If, as is suggested by some, the risk of suicide is increased by antidepressants, which are considered to be the cornerstone and most widely accepted treatment for depression, the use of such agents would obviously necessitate a critical re-evaluation.

Suicidality and suicidal actions induced de novo by SSRIs was suggested by a few clinical papers that followed Teicher's initial case report.⁴⁻⁶ Because of the paradoxical nature of these observations, a number of retrospective analyses of large cohorts were then conducted. The analyses of the US Food and Drug Administration database by Kahn et al⁹ looked at suicidality and suicide rates in a cohort of 23 201 patients partici-

pating in clinical trials of antidepressants. Overall suicide rates for patients were 627/100 000 compared with a general population rate of 11/100 000. There were no significant differences between rates for placebo, comparator drugs and new-generation investigational drugs. The mortality rates ranged from 0.19% for placebo to 0.14% for the investigational drugs and 0.11% for the active comparators. There were no significant differences in patient exposure years between these 3 groups, although the numerical values were higher for the antidepressant groups. The attempted suicide rate ranged from 0.66% for the investigational drugs to 1.37% for the comparators to 1.39% for placebo (no significant differences). Patient exposure years also did not differ significantly. These findings do not provide information on the duration of exposure to treatment but include the data on all patients who participated in the trials and are thus quite representative of short-term studies. Patient exposure years, which cumulates the duration of treatment and the number of patients treated, did not show differences either. These data do not support the suggestion that SSRIs add to suicide risk.

A similar study was done in the Netherlands by Storosum et al¹⁰ on data submitted to the Medicines Evaluation Board of the Netherlands for 12 246 patients treated in short-term (< 8 wk) clinical trials. Attempts at suicide occurred in 0.4% of patients in both placebo and active drug groups. Completed suicide occurred in 0.1% of patients in both placebo and active treatment groups. In longer-term studies (> 8 wk) involving 1949 patients, attempted suicide occurred in 0.7% of patients in both groups, and completed suicides occurred in 0.2% (2 patients) of the active drug group (no significant difference). These results also do not support a suicidogenic effect of these antidepressants.

Donovan et al¹⁷ reviewed 222 suicides that occurred in a 4-year period in 3 different regions of the United Kingdom. Of these, 83% had been diagnosed with depression in the past and 56% had been prescribed an antidepressant in the previous year; 41 had been prescribed a TCA and 13 an SSRI within 1 month of their suicide, and these formed the main cohort of the study. On the basis of the relative proportion of prescriptions in these regions, the authors concluded that the risk of suicide is greater with SSRIs than with TCAs. An important variable that may have skewed these findings is that those taking SSRIs included most of the patients

who had a recent history of deliberate self harm, which in itself is recognized as an important predictor of suicide. It is thus difficult to make any definitive conclusions from these findings because the inherent biases in patient selection for treatment force the results and conclusions.

More recently, Oquendo et al² reported on 136 depressed patients who were discharged from hospital after a major depressive episode and were followed in community settings for 24 months; 15% of patients attempted suicide during the 2 years, and 50% of these attempts occurred during the first 5 months of follow-up. Treatment was in a naturalistic setting and was monitored regularly. The medications administered were mainly the new-generation antidepressants. A critical review of the dosage administered considered it to be adequate in only 9 (43%) of the patients at the time of attempted suicide. Four of these patients had relapsed into a recurrence of depression. These findings elicit a number of questions such as the importance of treatment resistance, history of suicide attempts, components of adequate treatment, adequacy of drug treatment and compliance.

The case put forth in the first of this duo of papers is beguiling. It is indeed seductive to use legal precedents and the court of public opinion to evaluate the scientific merit and withdrawal of a therapeutic agent. However, it remains paramount that methodology not be changed to lead to selective data. For this reason, it is not appropriate in these instances to allow the bias introduced by separating placebo washout out of the trial data, especially if "intent to treat" and last observation carried forward data are to serve as the basis of outcome analyses.

It is not appropriate to agree with the statement that clinicians would not be vigilant to the risk of suicide in antidepressant RCTs, because suicide is universally recognized as the major complication of depression. Although antidepressant RCTs are not designed to evaluate suicide risk, disregarding the data generated is as inappropriate as disregarding the data collected for the study's designed purpose.

Discussion

SSRI antidepressants as a class are among the most frequently prescribed drugs in the Western world. Their applications have broadened from their initial indication in depression to a number of other psychiatric

conditions such as obsessive-compulsive disorder, generalized anxiety disorder and, more recently, late luteal phase disorder. This provides a wide spectrum of conditions under which the SSRIs are administered and allows for a much broader clinical experience for the appraisal of the drugs in question. There have not been any reports of suicide in patients taking SSRIs for these other conditions.

Suicide is a leading public health problem in all societies. It is estimated that known suicides account for 1 million deaths worldwide annually. Given that depression is a significant factor in nearly 50% of these cases, the treatment of depression merits critical appraisal, especially if this treatment contributes further to suicidal behaviour, as has been suggested. This partly explains the reaction to the initial reports of increased suicidality during treatment with fluoxetine and then with the other SSRIs. These reports have led to a healthy second look at the available data and to the pursuit of additional studies and observations.

Clinical studies and meta-analyses indicate that an overwhelming number of patients experience a decrease in suicidal ideation while taking SSRIs. The fact that these meta-analyses were based on data collected primarily to demonstrate efficacy does not diminish their validity. Although the method of evaluation has been criticized (i.e., a single item on the HAM-D) and the evidence of decreased suicidality admittedly not highly nuanced, the data still reflect the observed clinical reality. A decrease in suicidality must be considered to reflect an improvement in the depressed condition.

Despite the availability of less toxic antidepressant drugs, the increasing use of antidepressants has not consistently been associated with a significant decline in suicide rates. As the SSRIs gain popularity, the use of the older TCAs as instruments of suicide by overdose has decreased. However, other more violent means are resorted to, thus indirectly reducing the positive safety impact of the SSRIs. It would be simplistic to make conclusions on single causality in suicidal behaviour without recognizing the complexities of the behaviour and circumstances that lead to the outcome.

Although evidence from large studies points to a reduction in suicidal ideation, the few reports of the appearance of intense suicidal thoughts in a few patients must not pass unnoticed. There were sporadic reports of suicidality with zimelidine, the first SSRI. This did not hold up to statistical testing and, because the drug was discontinued shortly after being launched, there

was no follow-up. There were no major concerns at this time because most patients experienced an improvement in suicidal thoughts. A sporadic paradoxical effect to a psychotropic agent is a well-known phenomenon. It is well documented with antipsychotic agents such as the phenothiazines, where excitement and even worsening of the psychotic disorder have been observed. These are rare events but must be kept in mind so they will be recognized when they do occur.^{27,28} It is also essential to recognize that the emergence of suicidal thoughts may simply be attributable to underlying psychopathology.²⁹

Studies of fluoxetine have reported that this drug, in addition to causing some increase in agitation in some patients, may also cause akathisia. High levels of anxiety and agitation are known to accompany increased suicidal behaviour. In such a situation, the behaviour would be secondary to a side effect of the drug, rather than to its primary action.

Post hoc studies have intrinsic limitations but can shed some light on the understanding of this issue. The findings of Donovan and colleagues¹⁷ suggest that the increased risk of suicide is to a great extent explained by patient selection in some clinical studies. They did not factor in deliberate self-harm in the attribution of patients in their study. The increased risk of suicidality in patients with a history of repeated deliberate self-harm is well known. Even if these patients had been screened as not being actively suicidal at the onset of a trial, they were nevertheless still at higher risk subsequently. This type of susceptibility bias was very much present in the Leon et al study¹⁶ and in that by Donovan et al.¹⁷

A common deficiency in many studies of the treatment of depression is a consideration of unipolarity or bipolarity. The latter is readily missed for a number of reasons but, because the condition is not uncommon and requires adapted treatment with mood stabilizers, a greater risk of suicide may appear in these patients than in undertreated patients.

Despite anecdotal reports implicating most of the SSRIs, a drug-specific or class effect is not substantiated. Unfortunately, SSRIs have not been compared critically with other classes of antidepressants. On the other hand, the common pharmacological action of serotonin reuptake inhibition does not explain all of the actions of these drugs. A comparison of fluoxetine with its activating properties and citalopram with its more sedating profile illustrates the different effects SSRIs can have. Fluoxetine is known to occasionally cause

some agitation. This may be experienced independently from akathisia which may, albeit rarely, also result from fluoxetine. The combination of the 2 (i.e., akathisia and agitation) has been associated with increased suicidal tendencies in depressed patients, but it is unlikely that this would support a class effect or phenomenon. It is more likely a consequence of a rare side effect of the drug.

A pharmacological explanation for a rare event is difficult to establish because it is, by definition, unpredictable. However, it is not beyond the realm of possibility and merits further exploration, although it is unlikely to attract interest simply because of the rarity of the event and the unpredictability of a host of variables.

Conclusion

Any conclusions based on these few reports of sporadic cases of increased suicidality with SSRIs must be limited and highly tentative. The most these cases can suggest is an individual paradoxical effect, and these can be compared with the large number of patients who experience a diminution of suicidality and an improvement in depression. Another significant factor is that as the use of these antidepressants has broadened, the initial reports have not been followed by an increasing number of cases. Results of clinical studies are inconclusive, with some supporting a link and others refuting one. However, the awareness of the possibility of increased suicidality with SSRI treatment must be taken in the context of the risk of suicide in treating depression with any other antidepressant. Suicide is an inherent risk in the context of depression, but this should not deter from adequate treatment.³⁰

A review of this issue serves as a reminder of the basic principles of good therapeutics that recommend that the complete profile of the drug be taken into account when selecting a pharmacotherapeutic agent. Once the primary (desired) and secondary (unwanted or not) effects have been fully considered, the total profile of the drug can be tailored to the clinical profile of an individual patient.

The newer SSRI antidepressants were never considered to be superior in efficacy to the TCAs, but their entry into the therapeutics of depression has reduced the risk of iatrogenic intoxication and, most likely, the overall risk of suicidal outcome in adequately treated patients. There is, at this time, insufficient evidence to claim that they lead to suicide.

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