Suicidality with SSRIs – valid claim?

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Introduction

A proliferation of new antidepressants followed the introduction of the SSRIs with the associated claims of their relative innocuity compared to the previous generation of tricyclics (TCAs) and monoamine oxidase inhibitors (MAOIs). These claims seem to have reached their high point and are now undergoing a second phase of critical review. This reappraisal of antidepressants addresses not only the claims of the efficacy but also those related to side effects and 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 which would most likely not have come about otherwise. Invariably, in such circumstances, the pendular shift of attitudes can easily lead to exaggerated claims towards the negative and unwanted effects to the point of discarding previously demonstrated positive findings. At this time, there is a necessity of having 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 suicides 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 did lessen the risk somewhat but it still remained above the norm. (3)

One issue of considerable controversy has been the risk of suicide in relation to the SSRI class of antidepressants. The issue arose from a series of case reports of intense suicidal preoccupation and intense thoughts of self-harm while on antidepressant treatment. The initial response 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 randomised clinical 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 (7,8,9,10). This leads to the purpose of this duo of papers (Healy-Lapierre) where facts may be submitted to different views and interpretations.

The first questions which arise from this apparent temporal relationship is whether or not there is a cause effect relationship between the administration of a specific drug and the development of suicidal ideation. The order of such a cause-effect relationship may then be examined and attributed as either a primary drug effect, or as a paradoxical drug effect, or as an expected side effect of the drug or finally as an action which may be secondary to a side effect of the

compound. A second issue to be addressed is whether this effect is unique to a specific drug or one that is common to that class of drugs. The question of the validity of any imputed causality must be critically re-evaluated throughout this process. Once these issues are clarified, there may arise strategies that would improve the outcome of treatment for patients with depression.

Efficacy issues

Epidemiological observations suggest that there has been a gradual increase in the incidence of depression in the post-World War II generations. There are indications that this illness will become an ever increasing burden of disability in western societies (11). As 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 suicidal rates. Furthermore, if there is validity to the claim that SSRIs play a causative role in suicide, there would be an ever greater increase in suicide rates since the advent of these drugs. Although this may not have materialised as such, the question must not be dismissed outright as being invalid.

Epidemiological studies have been conducted on this issue in a number of countries. In Italy, there was found to be a possible relationship between increased SSRI utilization from 1988 to 1996 and rates of suicide. There was a slight increase in suicide rates for men but a more pronounced decrease for women, none of which were significant (12). In Sweden, there was a reported decrease in suicide rates from 1976 to 1996 in parallel to the increased utilization of antidepressants over this period of time (13). 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 tricyclic antidepressants. The tricyclics accounted for 82% of the suicides by antidepressant overdose (14) Ohberg et al 1998).

In the United States, Fluoxetine was targeted in the NIMH Depression Study data base by Leon et al (15). This was an attempt to shed some light on the possibility of an increased suicidal risk associated with that specific SSRI. In the 185 patients in follow-up, there was a trend for a decrease in the number of suicide attempts compared to patients receiving other treatments. As this cohort was at higher risk because of a previous history of repeated suicide attempts, treatment with fluoxetine resulted in a significant reduction of these.

The main sources of information on psychopharmacological agents are the data compiled in the clinical trials. These are designed to primarily demonstrate the efficacy of a new drug. Then, the post-marketing studies are intended to provide the alerts on safety and potentially new indications for drugs. Both of these sources have limitations and biases which eventually contribute additional arguments to the debate.

As randomised clinical trials (RCTs) are designed to primarily identify clinical efficacy of antidepressants, there are limitations on the gathering of exhaustive data on unwanted side effects. The selection of patients for a RTC generally excludes patients who are considered to be at risk for suicide. This is usually determined clinically and the judgement is based on clinical indicators which have in past experience been associated with increased risk. Up to 80% of depressed patients may experience thoughts of suicide added to the greater than 15% risk of suicide in depression, the elucidation of suicidal thoughts and intent is increasingly relevant to a valid assessment of risk. This is done on the premise that suicidal ideation is the precursor of suicidal acting out. Suicidal acts in the recent past as well as a number of other associated factors all contribute to the elevation of risk and the decision of inclusion or not. This inevitably leads to a skewed population where those mostly clearly at risk and those more severely depressed are often excluded (7).

The experimental design most often utilized is that of a single blind placebo washout phase followed by a double-blind randomised 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 to having unbalanced groups with fewer subjects in the placebo and control arms. This results in reduced power and the need for larger numbers of patients in the studies. This has led to increasing numbers of multicentre trials (MCTs).

The end point of a RCT is time limited and the criteria of successful outcome are based on clinical evaluations which of necessity are quantified using rating scales and focus on the immediate objective. They then have limited retrospective applicability and have intrinsic limitations when explored subsequently for other purposes. This does not necessarily invalidate subsequent retrospective studies.

A similar bias occurs in post-marketing surveillance studies. Clinicians are known to adopt different prescribing patterns for patients presenting more severe states of depression and also for patients who are considered as being at greater risk for suicide. The former group are more likely to receive a TCA while the latter group are more likely to receive the "safer in overdose" SSRIs. Thus a significant bias in patient selection arises in the evaluation of suicidal risk under one form of treatment or another (16).

Suicidality and suicide must be distinguished. Thoughts of suicide are not uncommon in the general population but become problematic if too frequent, intense or commanding with subsequent greater risk of acting out of the ideation. Most suicides are preceded by increases in suicidal ideation. Thus, this becomes an important consideration in the assessment of suicide risk. Conditions favourable to acting out the behaviour especially increased impulsivity

increase risk. On the other hand, suicidal ideation as such cannot be totally equated to suicidal probabilities.

The suicidal tendencies item of the Hamilton Depression Scale for Depression is the instrument for quantification (18). 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. It does allow for a certain degree of quantification on the seriousness of the suicidal tendencies and emphasises mainly the suicidal ideation as such. However as it is probably the most widely used rating scale for RCTs on depression, it has become the standard instrument for the analysis of the many features of this illness and the change at different intervals during a clinical trial.

Meta-analyses of RCTs have yielded conflicting results. The short duration of RCTs may not prove valid long-term data but they do contribute to an understanding of acute therapeutic effects. There is an inherent deficiency in each of these studies because of the intrinsic limitations of such post-hoc analyses. Nevertheless, there were a few of these studies which suggested that fluoxetine was associated with a greater incidence of suicidal thoughts. This was followed by other studies suggesting that sertraline, fluvoxamine, paroxetine and citalopram produced similar effects (4,5,6,19). This leads to the speculation of a class effect of SSRIs. On the other hand, there are meta-analytic and other types of studies which suggest that emergent suicidal ideation was lessened by these same SSRIs (20,21). Others have suggested that not only do SSRIs reduce suicidal ideation but that this symptom is increased in association with treatment with NE reuptake inhibitors (22). A meta-analytic study of treatment with fluoxetine, tricyclic antidepressants and placebo in large samples of patients with mood disorders and in nearly as many without mood disorders did not identify any difference in emergent suicidal thoughts in any of the groups for both groups and no suicides in the absence of mood disorder (23).

Firm conclusions on suicidality and SSRIs based on these findings must be guarded at this point. Suffice it to say that there is evidence to suggest that SSRIs generally reduce suicidality in most patients. However, there may be a subgroup of patients who react differently with an increase in suicidal ideation.

Suicide

Suicide with prescribed antidepressants has been a longstanding concern to clinicians treating depressed patients. This was particularly significant with older generation tricyclics (24,25). This in itself was sufficient reason to advocate the use of newer agents because of their reported lower lethal potential in overdose. On the other hand, it is surprisingly rare for patients to use their prescribed antidepressants for suicidal purposes. Data on agent for suicide from a number of countries suggest that about 5% of overdoses are with antidepressants and this ranges from 1% to 8%. An outlier appears to be the United Kingdom with reports of 14% (17). Men use overdose as a method of suicide much less

frequently than women. Furthermore, it appears that patients tend to use previously prescribed undiscarded antidepressants as their drug of choice. This finding points to the role of therapeutic failure in the number of suicides which suggests a treatment failure with previous treatment strategies.

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 to publicize the profile of the new antidepressants in their treatment. This, in addition to other factors, is responsible for a large part of this teaching to have been sponsored by the pharmaceutical industry. These efforts have certainly contributed to a heightened awareness professionals and to less reluctance in the use of antidepressants because of improved safety profiles with equivalent efficacy.

Although antidepressants have been pivotal in the treatment of depression for more than four decades, there are still a number of unanswered questions. Their therapeutic superiority has been taken for granted in spite of the inconsistent robustness in many controlled studies with variable superiority over placebo in many instances. Recent data on the latest generation of antidepressants, the SSRIs and SNRIs suggest that only 48% of placebo controlled studies demonstrate a consistent statistically significant superiority of the antidepressant over placebo (8). These findings emphasise the need for individualised therapeutic strategies when treating patients. This becomes critical for poor responders where the efficacy and limitations of available treatments become obvious. Depression is the main risk factor for suicide which in turn is the final and fatal outcome of non-response to treatment. If, as suggested by some, the risk of suicide is increased by antidepressants the 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 SSRI antidepressants was suggested by the early clinical reports mentioned earlier (4,5,6). A number of retrospective analyses of large cohorts were done to shed some light on these issues. The analyses of the FDA database reported by Khan et al (9) looked at suicidality and suicide rates in a cohort of 23,201 patients participating in clinical trials of antidepressants. Overall suicide rates were found to be 627/100,000 compared to a general population rate of 11/100,000. There was no statistical difference between placebo, comparator drug and new generation investigational drug. The mortality rates ranged from 0.19% on placebo to 0.14% for the investigational drug and 0.11% for the active comparator. Analysis of the patient exposure years (PEY) did not show statistical differences between these three 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 comparator to 1.39% for placebo, the differences not being significant. Analysis of PEY 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 is thus quite representative of short-term studies.

This study was replicated by Storosum et al (10) on the data submitted to the Medicines Evaluation Board of the Netherlands for 12,246 patients treated in short term (<8 weeks) clinical trials. Attempts at suicide occurred in 0.4% of patients in both placebo and active treatment groups. In the longer-term studies (> 8 weeks) involving 1,949 patients, attempted suicide occurred in 0.7% of patients in both groups and completed suicides occurred in two patients (0.2%) of the active drug group. This was not statistically significant.

By tackling the issue from the suicide outcome, Donovan et al (16) reviewed the data on 222 suicides which occurred over a 4 year period in three different regions of the United Kingdom. Of these, 83% had a diagnosis of depression in the past and 56% had been prescribed an antidepressant in the previous year. Forty one had been prescribed a TCA and 13 an SSRI within one month of their suicide and these formed the main cohort of the study. Based on the relative proportion of prescriptions in these regions for the two classes of drug, they conclude that the risk of suicide is greater with SSRIs than with TCAs. An important variable which may skew the findings is that those on SSRIs included most of the patients who had a recent history of deliberate self-harm (DSH) which in itself is recognised as an important predictive variable to suicide.

More recently, Oquendo et al (2) followed up on 136 depressed patients discharged from hospital following a major depressive episode and followed up in community settings for 24 months. 15% of these attempted suicide during the two 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 at adequate levels 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, previous history of suicide attempts, components of adequate treatment, adequacy of drug treatment and compliance.

Discussion

SSRI antidepressants as a class are among the most frequently prescribed drugs in the western world. Their application has broadened from their initial indication in depression to a number of other psychiatric conditions such as obsessive-compulsive disorder, generalised anxiety disorder and more recently to late luteal phase disorder. This provides a wide spectrum of conditions under which the SSRIs are administered and follows for a much broader clinical experience for appraisal of the drugs in question. There have not been 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 recognised suicides account for 1 million deaths worldwide annually. As depression is a significant factor in nearly 50% of these, 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 treatment with the other SSRIs. These reports have lead to a healthy second look at the available data and to the pursuit of additional studies and observations. There are overwhelming numbers of patients who have experienced a decrease in suicidal ideation while under treatment with SSRIs as becomes apparent in a number of metanalyses. Even though these metanalyses were based on data collected primarily for the demonstration of efficacy, this dose not diminish their validity. Although there has been criticism of the method of evaluation as a single item of the HAMD the evidence of decreased suicidality admittedly not highly nuanced, still reflects the observed clinical reality. A decrease in suicidality must be considered to be a reflection of improvement in the depressed condition.

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

The sporadic reports of the appearance of intense suicidal thoughts in a few patients must not pass unnoticed in spite of the evidence from large studies which point to a reduction of this same phenomenon. There were sporadic reports of suicidality with zimelidine, the first SSRI. This did not hold up to statistical testing and, as the drug was discontinued shortly after being launched, there was no follow-up. As most patients had experienced an improvement in suicidal thoughts, concern did not arise at the time. The appearance of 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 has been observed. These are rare events and must be kept in mind for them to be recognised when they do occur (26,27,28).

The reports with fluoxetine have implied that this drug, in addition to causing some increase in agitation in some patients, may also cause akathisia as a specific effect resulting in a further increase in agitation. High levels of anxiety are recognised as accompanying increased suicidal behaviour.

Post-hoc studies have intrinsic limitations but can shed some light in the understanding of this issue. The findings of Donovan suggest that the increased risk of suicide is to a great extent explained by patient selection in clinical studies. These did not factor in deliberate self harm (DSH) in the attribution of patients. The increased risk of suicidality in patients with a history of repeated DSH is well known such patients. These patients had been screened as not being actively suicidal at the onset of a trial but were nevertheless at higher risk subsequently.

The question of a drug specific or class effect is not defined in spite of anecdotal reports implicating most of the SSRIs. Unfortunately, this has not been compared critically to other classes of antidepressants. On the other hand, a common pharmacological action serotonin reuptake inhibition does not explain the totality of actions of a drug. A comparison of fluoxetine with its activating properties and citalopram with its more sedating profile illustrates the contrasts of effect on patient behaviour that two SSRIs can exert. Fluoxetine is known to occasionally cause some agitation. This may be experienced independently from akathisia which may, albeit rarely, result from fluoxetine. The combination of the two ie. akathisia and agitation has been associated with increased suicidal tendencies in patients with depression. It is unlikely that this would support a class effect or phenomenon. It is in this situation much more likely a consequence of a rare side effect of the drug.

A pharmacological mechanism that can explain a rare event is difficult to establish as it, by definition, is not predictable. 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 the host variables.

Conclusion

Any conclusion based these few reports of rare sporadic cases of increased suicidality with SSRIs must be limited and highly tentative. The most these cases can suggest is an individual paradoxical effect. These rare cases are contrasted to the large numbers of patients who experience a diminution of suicidality as well as improvement in depression. Another significant factor is that the initial reports have not been followed by increasing numbers of cases as the use of these antidepressants has broadened. The variations in the incidence of suicide in clinical studies are inconclusive as there are as many studies with differences which point in one direction as in the other.

The awareness of the possibility of increased suicidality with SSRIs must be taken in context with the risk of suicide with other antidepressants. As a worst case scenario, it is a rare event to be kept in mind but its occurrence is more likely in the context of depression where suicide is an inherent risk. This should not deter from adequate treatment which in itself adds to the risk of lethality (29).

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

The newer antidepressants were never considered as superior in efficacy to the TCAs but their entry in the therapeutics of depression has reduced the risk of iatrogenic intoxication and most likely the overall risk of suicidal outcome in adequately treated patients.

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