COMMENTARY

Drug Saf 2011; 34 (5): 397-401
0114-5916/11/0005-0397/$49.95/0

Getting Through the Quicksand of the Relationship between Drugs and Suicide

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A variety of study designs have been employed to investigate whether exposure to some drug treatments, including antidepressants and antipsychotics, may have a beneficial or harmful effect on the risk of committing suicide. In this commentary, basic considerations that may help critically evaluate the literature on drugs and suicide are discussed, with specific emphasis on the role of experimental and observational studies in deciphering this association.

In this issue of *Drug Safety*, Gibbons and Mann[1] reviewed the literature on methodological and statistical approaches to the design and analysis of studies that attempt to establish an association between drug exposure and the risk of suicide. In addition, Gibbons and Mann[1] analysed the most recent literature on the relationship between some drugs and suicide-related outcomes.

This compelling and comprehensive article provides readers with such a large amount of information on study designs, individual drugs, statistics details and methodological considerations that sometimes readers might have the feeling of being stuck in the quicksand. The present commentary aims at raising awareness on a minimum set of key issues that may be helpful in deciphering the Gibbons and Mann[1] review and, more generally, in critically appraising the literature on drugs and suicide.

1. Be Aware of the Outcome of Interest

Ideally, studies investigating whether drug exposure increases the risk of suicide should use completed suicides as the outcome of interest. Completed suicide is, however, a rare event, and studies often employ proxy and composite measures that combine completed suicides with attempted suicides, preparatory acts, suicidal behaviour and suicidal ideation. In the US FDA re-analysis of randomized trial data, described by Gibbons and Mann,[1] 372 placebo-controlled antidepressant trials and nearly 100 000 patients were included, but only eight completed suicides were recorded.[2,3] As a consequence, in order to increase the power of analysis, a hierarchical model of outcomes of interest was developed, with death by suicide at the top, followed by suicide attempt, preparatory acts toward imminent suicidal behaviour, suicidal ideation, self-injurious behaviour (intent unknown), not enough information (with fatal outcome) and not enough information (with non-fatal outcome). The FDA analysis considered, as the primary outcome, suicidal ideation or worse, including preparatory acts, suicide attempts and completed suicides. Clearly, while this choice seems a reasonable compromise in order to have enough statistical power, it leaves us with some uncertainty, because the extent to which the concept of suicidal ideation is linked with the risk of death by suicide is unknown. A second reason for concern is that suicidal ideation is self-reported rather than observed by others; therefore, it is possible that some individuals may have suicidal ideas but do not want to express them, or may be in a condition that does not allow them to be open about these thoughts and ideas. This may underestimate the frequency of this outcome measure

and, more crucially, may constitute a potential source of bias, as reporting may theoretically differ according to sociodemographic or clinical variables.

Action: Always check what the outcome is, and how it was assessed.

2. Be Aware of the Background Hypothesis

The relationship between drug exposure and suicide risk should be analysed taking into account that some conditions, for example mental disorders, are themselves associated with this negative outcome. It must be very clear, therefore, that for some drugs the background hypothesis is that drug exposure may decrease the risk of suicide by having a beneficial impact on the underlying condition. In this case, suicide is an outcome measure that may be positively affected by drug treatment. This applies, as reported by Gibbons and Mann,[1] to the relationship between antipsychotic drug exposure and suicide in individuals with schizophrenia, where a protective role of drug treatment has been suggested, and current debate focuses on which antipsychotic drugs are more effective in reducing the risk of suicide associated with schizophrenia.[4] By contrast, for some other drugs the background hypothesis is the possibility that drug exposure itself may cause the emergence or worsening of suicidal ideas in vulnerable patients. In this case, the risk of suicide may be better conceptualized as an unwanted adverse effect of drug treatment. Gibbons and Mann[1] reported the example of antidepressants, where, paradoxically, instead of debating which drugs are more effective in reducing the risk of suicide by treating the depressive symptoms effectively, much current literature focuses on which antidepressants are less dangerous in causing suicide.

Action: Check if suicide is investigated as an unwanted adverse effect of drug treatment.

3. Systematic Reviews of Randomized Evidence

The review by Gibbons and Mann[1] highlighted the contribution of randomized evidence in shedding light on the compelling issue of whether antidepressants increase the risk of suicide. Single trials do not have enough statistical power to establish associations, but systematic reviews and meta-analyses of clinical trial data, by pooling together information from hundreds of studies, have been able to increase statistical power and provide more precise estimates. However, it has been well documented that the value of systematic reviews and meta-analyses rely on their ability to include the vast majority of studies (theoretically all studies) meeting the inclusion/exclusion criteria, with specific emphasis on unpublished trials. Suicide is a rare event, and the systematic exclusion of few unpublished trials has been shown to completely bias the overall estimates.[5]

Action: Don't rely upon the single trial and check if unpublished trials have been searched and included in systematic reviews.

4. Systematic Reviews of Randomized Evidence: Individual Patient Data can Make the Difference

There are a variety of ways to collect data from randomized trials and bring them together in a statistical synthesis. These include extraction of data from published reports, collection of aggregate data from the responsible investigators, or collection of individual patient data from the investigators.[6,7] The latter methodology allows for the collection of information on clinically meaningful variables relating to the individual patient (sex, age, severity of illness) and to specific outcomes of interest (e.g. suicide-related events). Statistical re-analyses may therefore be carried out using commonly defined subgroups in order to ascertain whether some variables act as moderators of treatment effect. For example, the FDA meta-analysis included nearly 400 placebo-controlled antidepressant trials, and for each of these trials patient-level data were collected, yielding a database of nearly 100 000 patients.[2,3] Using individual patient data, it was possible to show that the relationship between antidepressant drug treatment and the incidence of reported

suicidal behaviour in clinical trials was strongly related to age; the risk associated with drug treatment relative to placebo was found to be elevated in subjects under 25 years of age, neutral in subjects aged 25–64 years (reduced if suicidal behaviour and ideation are considered together) and reduced in subjects aged 65 years and older. The FDA analysis clearly indicated that age must be taken into account as a moderator of treatment effect. A traditional meta-analysis of aggregate data would not have had the possibility of producing this information.

Action: Check if patient-level data were obtained; if yes, check if moderators of treatment effect were detected.

5. Observational Studies May Offer Key Insights

A controversial point of the FDA analysis is that the included trials were not primarily designed to measure suicidality. Considering that it is unlikely that individual randomized trials will be designed to primarily investigate the effect of antidepressant use on suicidality, and that future systematic reviews of clinical trial data will not be able to overcome the limitations of the FDA analysis, it has been suggested that randomized evidence be supplemented with observational evidence. Observational studies typically employ hard outcomes such as suicide attempt (which is something more articulated than preparatory acts) and completion, moving away from the controversial concept of suicidality or suicidal ideation. In 2009, the results of a meta-analysis of eight large-scale observational studies that compared the risk of suicide among patients with depression who received SSRIs and those with no exposure to antidepressants were reported.[8] Similarly to the FDA analysis, the re-analysis of observational data found that the relationship between exposure to SSRIs and the risk of suicide was influenced by age. Exposure to SSRIs decreased the risk of suicide by over 40% among adults and over 50% among elderly people. However, among adolescents, exposure to SSRIs almost doubled the risk of suicide. Clearly, observational studies have limited ability to adjust for baseline differences and are prone to bias and confounding, but they typically include large populations followed under naturalistic circumstances, thus offering an added dimension in the evaluation of drug safety that is complementary to that provided by clinical trials.

Action: Check if results of observational studies are coherent with randomized evidence.

6. Single Trials and Single Epidemiological Studies May Have a Role (a Key Role)

In section 3 the notion that single trials do not have enough statistical power to establish associations between drug exposure and suicide risk was highlighted, but this may not always be true. In 2003, the protective role of clozapine versus olanzapine in terms of suicide attempts was investigated in a multicentre, randomized, international, 2-year study that enrolled 980 patients with schizophrenia or schizoaffective disorder.[9] It found 34 attempted suicides in those receiving clozapine and 55 in those receiving olanzapine. This yielded a hazard ratio of 0.76 (95% CI 0.58, 0.97; $p = 0.03$) in favour of clozapine. The results of this randomized trial were more recently confirmed by an epidemiological study that compared the cause-specific mortality in 66 881 patients with schizophrenia versus the total population in Finland (5.2 million).[4] It found that long-term treatment with antipsychotic drugs is associated with lower mortality compared with no antipsychotic use, and clozapine seems to be associated with a substantially lower risk of death from suicide than any other antipsychotics.[4]

Action: Don't rely upon the single trial, but if single trials are powered to primarily assess the relationship between drug exposure and suicide risk then pay due attention.

7. Ecological Studies May be Misleading

A number of ecological studies have been conducted in different countries to investigate the

relationship between antidepressant prescribing and suicide. Gibbons and Mann[1] showed that most of these ecological analyses found that the decline in suicide rates observed in several countries appeared to be associated with greater use of new generation antidepressants; however, almost all these studies looked at short-term trends. This is a crucial factor because it is possible that suicide rates were already declining before the dramatic rise in antidepressant prescriptions. Focusing on 10 or 20 years only might give the wrong impression of an association between antidepressant prescribing and suicide rates while, in reality, the outcome of interest (decreasing suicide rates) might have preceded the exposure variable (antidepressant prescribing). In Italy, for example, the analysis of long-term trends in suicide did not suggest that increases in antidepressant prescribing lie behind recent reductions in population suicides.[10]

Action: Be very sceptical if ecological studies claim evidence of 'significant' associations.

8. No More Quicksand?

These considerations lead to the general concept that the assessment of the relationship between drugs (exposure variable) and suicide (outcome variable) may benefit from the contribution of both experimental and observational studies.[11] Although a compelling debate goes on in the literature on whether the hierarchy of evidence that is generally applied to the *intended effects of drugs (efficacy)* should similarly be applied to the *unintended effects of drugs (adverse effects)*,[12] from the perspective of the interested reader a pragmatic approach to get through the quicksand of this association is to consider that the issue of whether experimental evidence should be top of the hierarchy may not be that relevant. What is relevant is that single trials designed to establish efficacy are not useful as suicide is a rare outcome, but systematic reviews of clinical trials may overcome the power issue (figure 1). Additionally, individual randomized studies primarily designed and powered to assess the relationship between drugs and suicide should always be taken into careful consideration. The contribution of observational studies is similarly relevant (figure 1) as individual observational studies may have the power to establish significant associations, and re-analyses of systematically collected compilations of studies may be used to generate observational evidence that may confirm or confute the evidence generated in experimental settings.

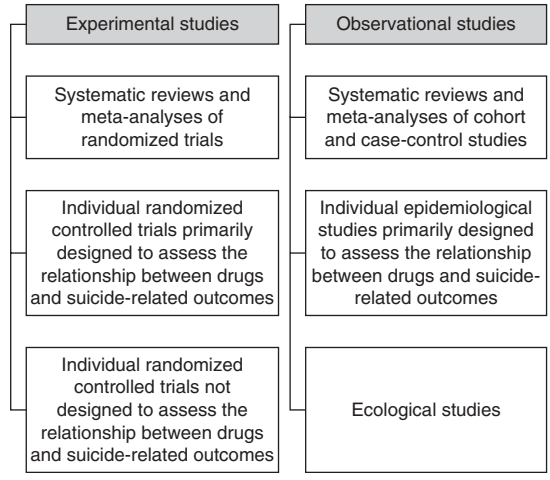

Fig. 1. Contribution of different study designs to the assessment of the relationship between drug exposure and suicide risk (see text for further explanation).

Acknowledgements

No sources of funding were used to prepare this commentary. The author has no conflicts of interest to declare that are directly relevant to the content of this commentary.

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