

In debate

The increased use of antidepressants has contributed to the worldwide reduction in suicide rates

Göran Isacsson & Charles L. Rich / Jon Jureidini & Melissa Raven

Summary

Numerous ecological studies have shown an inverse association between antidepressant use and suicide rates and a smaller number of individual-based studies have shown an association between current antidepressant use and reduced suicide risk. Such evidence is often cited in support of the notion that antidepressants prevent suicide. However, more recently, the premises underlying this proposition, namely that suicide is caused by depression and that antidepressants relieve depression, have been challenged and the potential harm caused by

antidepressants has been highlighted. In this article, Goran Isacsson and Charles Rich debate with Jon Jureidini and Melissa Raven the motion that the increased use of antidepressants has contributed to the worldwide reduction in suicide rates.

Declaration of interest

G.I. has received fees from several companies selling antidepressants; C.L.R.: none / J.J. & M.R. are members of Healthy Skepticism.

For

Suicide rarely occurs in the absence of depression.^{1,2} Therefore, the hypothesis that suicide might be prevented by the treatment of depression is not far-fetched.

The total use of antidepressants in Sweden in 1990 was sufficient to treat less than 1% of the population, whereas the prevalence of depression was around 5%. Toxicological investigations of suicides in 1990–91 estimated that this amount of treatment prevented around 100 suicides annually in Sweden. It was suggested that the use of antidepressants had to increase fivefold if suicide rates were to be lowered by 25%.^{3,4}

By 1996, suicide had decreased in Sweden by 19% concurrent with a 3.4-fold increased use of antidepressants. Similar inverse associations were also seen in Norway, Denmark, Finland, Hungary and the USA. Consequently, this was described as a 'medical breakthrough' in the prevention of suicide.^{5,6} Since then, 21 ecological studies with different designs replicated this inverse correlation.^{7–9} These studies presented data from Australia, Sweden, Denmark, Finland, Great Britain, Hungary, Israel, Italy, Japan, New Zealand, Norway, Slovenia and the USA, as well as from across 27 other countries. Only one study from Iceland (population 285 000) failed to demonstrate a decrease in suicide parallel to an increase in the use of antidepressants. Also worth noting is the increase in child suicide in the USA coinciding with a decrease in the prescribing of antidepressants to children following the Food and Drug Administration (FDA) warnings.¹⁰

The possibility that this association is spurious cannot be ruled out by ecological study.

However, no good alternative explanation for the decreases in suicide has been claimed or supported by data. To prove causality, the individual exposure to antidepressants has to be ascertained. It is meaningless to demand randomised clinical trials, since such studies are impossible for statistical and ethical reasons. Observational study with scientific standards is therefore necessary to provide empirical data which either increase or decrease the plausibility that the hypothesis is true.

There is also an increasing number of individual-based studies providing evidence that the decrease in suicide has indeed occurred among individuals who were exposed to antidepressants.

Utilising a national prescription database in Denmark, Söndergård *et al* found that the more antidepressants dispensed to an individual, the lower the individual's risk of suicide.¹¹ Jick *et al* demonstrated in a controlled study of the UK General Practice Research Database that the relative risk for suicide was 38 times higher in those prescribed an antidepressant 1–9 days before suicidal behaviour compared with those who were prescribed an antidepressant 90 days or more before.¹² Angst *et al* found that in a 40- to 44-year Swiss follow-up study the standardised mortality ratio for suicide was 13.8 for individuals treated with antidepressants *v.* 33.3 for untreated individuals.¹³ In Finland, Tiihonen *et al* found that, among those who attempted suicide who had ever used an antidepressant, the current use of medication was associated with a markedly decreased risk of suicide.¹⁴ Our group recently published a controlled individual-based study of forensic toxicological screenings of 16 937 suicides in Sweden between 1995 and 2005.¹⁵ We found that the trend in the detection of antidepressants over the 11 years was what would be expected if the decrease in suicide had occurred among individuals treated with antidepressants.

There is undoubtedly a unique chain of various causal factors behind each individual suicide.

Most people who die by suicide have one factor in common however – depression.

Consequently, a large amount of evidence has accumulated over the years supporting the hypothesis that treatment with antidepressants prevents suicide.

Göran Isacsson & Charles L. Rich

Against

Like most who claim that increased use of antidepressants has contributed to reductions in suicide rates, Isacsson & Rich's interpretation of evidence is shaped by the following deductive reasoning:

- suicide is caused by depression (premise 1)
- depression is relieved by antidepressants (premise 2)
- therefore antidepressants prevent suicide.

However, both premises are flawed. Premise 1 privileges depression over many other potential contributors to suicide, both

proximal (e.g. alcohol intoxication, acute interpersonal conflict, access to lethal methods) and distal (e.g. poverty, unemployment). The strongest support for Isacsson & Rich's statement that 'suicide rarely occurs in the absence of depression' comes from psychological autopsy studies. However, their methodology is problematic.¹⁶ Relatives often seek relatively socially acceptable explanations, and may be unaware of or unwilling to disclose certain problems, particularly those that generate shame.¹⁷ Additionally, a psychiatric history would increase the likelihood of an ambiguous death being classified as suicide. Even so, one of Isacsson & Rich's own studies found that only 36% of individuals had depression,² as did Zonda, who argued that depression is overemphasised to the neglect of more commonly found psychosocial factors and severe somatic disease.¹⁸

Premise 2 is undermined by the fact that antidepressants are not very effective at treating depression. The evidence is weak that antidepressants improve scores on depression rating scales to a clinically significant degree, let alone improving substantive long-term outcomes.¹⁹

Nevertheless, we agree that 'the hypothesis that suicide might be prevented by the treatment of depression is not far-fetched'. However, Isacsson & Rich have failed to produce robust evidence for their much stronger claim that 'treatment with antidepressants prevents suicide'.

Most evidence used to argue that antidepressants reduce suicide comes from ecological studies. Unfortunately, many commentators conflate correlation with causation, and ignore the heterogeneity of diagnoses for which antidepressants are prescribed. In addition, many ecological studies focus on short time periods, ignoring decreases in suicide rates preceding the introduction of selective serotonin reuptake inhibitors (SSRIs)²⁰ and fluctuations in suicide rates over time in response to socio-economic, cultural and religious factors.²¹ Most studies fail to consider that increased antidepressant consumption may reflect chronic use rather than more users.²² Few ecological studies move beyond crude correlations. Of those that do, one found no association between antidepressant prescribing and suicide after adjusting for gender, age, year, and proportion of prescriptions for SSRIs.²³ Another, controlling for gender, age, county-level variations, unemployment and alcohol consumption, found a positive relationship between antidepressant use and suicide in young people.²⁴

Isacsson & Rich's claim that only one ecological study has not found decreased suicide rates paralleling increased antidepressant use ignores these and several other contrary studies.^{20,25,26} Their claim that increases in child suicide coincided with decreased antidepressant prescribing has been refuted.²⁷ However, we agree with their conclusion that ecological studies cannot settle this debate.

Isacsson & Rich cited five individual-based studies that provide stronger evidence than ecological studies. However, there are problems with these studies and Isacsson & Rich's interpretation of them. First, they claim that Søndergård *et al* 'found that the more antidepressants dispensed to an individual, the lower the individual's risk of suicide'.¹¹ In fact, 1995–1999 suicide rates in Denmark decreased for both antidepressant users and non-users. Unlike many studies, this one acknowledged the possible contribution of non-pharmacological factors (e.g. restriction of the availability of paracetamol) to the decrease in suicide. Second, Jick *et al*'s¹² finding that the relative risk for suicide was 38 times higher in those treated with an antidepressant for 1–9 days *v.* 90+ days does not unequivocally support a protective effect. Instead, as they acknowledged, it could be because of natural fluctuations in depression severity or because antidepressants worsen depression in the short term. Third, Angst

et al's participants were seriously ill hospitalised patients, 61% of whom had psychosis. As they noted, it is inappropriate to generalise from such patients to people with depression in general.¹³ Tiihonen *et al* also focused on patients admitted to hospital because of suicide attempts.¹⁴ The more antidepressants used prior to hospitalisation, the higher the risks of suicide, suicide attempts, and mortality during follow-up, a finding not necessarily attributable to confounding by severity. Also, patients using antidepressants during follow-up had significantly higher rates of suicide than people who never used them.

Finally, as in most suicide toxicology studies, Isacsson *et al*¹⁵ did not consider the possibility of suicide being triggered by antidepressant withdrawal, which is not detectable by toxicological screening. Furthermore, the study fails to take account of the correlation between decreased official suicide rates and decreased autopsy rates and increased ill-defined death rates in Nordic countries.²²

In summary, Isacsson & Rich's premises are flawed and they have overstated their case with selective citation and biased interpretation of evidence.

Jon Jureidini & Melissa Raven

For: Rebuttal

Jureidini & Raven are sceptical of two premises: (1) suicide is caused by depression; and (2) depression is relieved by antidepressant medication. Both of these premises are supported by large bodies of evidence. Neither is a necessary condition, however, for our proposition that treatment with antidepressants prevents suicides. However, we believe that they offer the most plausible mechanism to explain how antidepressants would prevent suicides. Thus they form the logic behind our conclusion. It is also perfectly possible to postulate that antidepressants have direct antisuicidal effects. It is equally reasonable to posit indirect antisuicidal effects by improving the ability of a person with depression to maintain social relationships, employment and sobriety. None of these effects would be mutually exclusive.

As we stated in our opening argument, the criticisms Jureidini & Raven present to the evidence we cited in support of our conclusion are perfectly legitimate. There will never be indisputable evidence that any intervention prevented a suicide since a non-suicide is a non-event. Even rigidly controlled experimental studies may be disputed as demonstrated by Jureidini & Raven. Of course, naturalistic studies are more subject to dispute. Regardless, we wish to do something to prevent suicides in the absence of definitive proof, and we believe the weight of evidence points at the treatment of depression with antidepressants as an important strategy. We do not know how Jureidini & Raven define the term 'robust evidence' so we cannot respond to their call for it.

We previously concluded, 'There is undoubtedly a unique chain of various causal factors behind each individual suicide.' Clinical science is, however, more about finding generalities that identify practical targets for intervention in a population. Jureidini & Raven imply that reducing alcoholism, somatic disease, interpersonal conflicts, access to lethal methods, poverty and unemployment would prevent suicides. This might very well be true. It is, however, a daunting task to come up with suitable interventions along these lines. Then there remains the challenge of finding evidence, 'robust' or otherwise, for the effectiveness of proposed interventions.

Jureidini & Raven suggest that we have ignored three ecological studies that had not found inverse correlations between antidepressant use and suicide rates. Two of the three studies are from Italy. The first studied trends from 1988 to 1996 during

which time the sales of antidepressants increased by 53%, and suicide rates increased by 4% in men and decreased by 18% in women.²⁵ The second studied trends during 1983–2000 when sales increased by 236%, paralleled by decreases of suicide rates by 22% in men and by 35% in women.²⁶ We did not include these two studies because of low-quality exposure data. In a newer study from Italy²⁸ with individual-based data for the period 1997–2006, the number of individual users increased by 376% and the suicides rates decreased by 34%. We think it is fair to say that the inverse correlation has been demonstrated also in Italy. The third study provides no data on the use of antidepressants and therefore adds nothing to this issue.²⁰

Besides low-quality (or absent) exposure data, a failure to demonstrate a correlation may also result from limited statistical power. With this in mind, we cannot agree with Jureidini & Raven when they claim that the study by Gibbons *et al*²⁹ that found 248 more suicides (+14%) among 5- to 19-year-olds in the USA in 2004 compared with 2003 is 'refuted' by Wheeler *et al* who found four more suicides among 12- to 17-year-olds in the UK in 2004 compared with 2003, and 10 fewer in 2005.²⁷ Those numbers are too small for any conclusions.

Jureidini & Raven also criticise the use of 'crude rates' in ecological studies and favour 'adjusted rates'. That may sound intriguing, but each variable that is introduced as a covariate includes an assumption that the variable influences suicide rates (causality). Introduction of irrelevant covariates might obscure true 'crude' rates. One example of such irrelevant variables is 'decreased autopsy rates' as demanded by Jureidini & Raven. Clinical autopsy has indeed decreased but, at least in Sweden, suicide is investigated by means of forensic autopsy, which has not decreased. Neither is the decrease in suicide offset by an increase in 'ill-defined' death. Contrary to Jureidini & Raven's claims, the latter has decreased even more than suicide. In summary, we believe our basic premises are backed by solid science, our selected citations are comprehensive, and our interpretation is fair.

Göran Isacson & Charles L. Rich

Against: Rebuttal

Without adding significant evidence, Isacson & Rich reassert that antidepressants prevent suicide. We agree that it is difficult to intervene with the important contributors to suicide (notwithstanding a range of successful public health interventions).³² We disagree that this justifies promoting antidepressants, unless they are proven helpful – doing nothing is better than doing something useless or harmful. Given the weak evidence for clinically meaningful effectiveness of antidepressants, we cannot ignore suggestive evidence of serious harm. Randomised controlled trials are not designed and powered to detect suicidal behaviour and routinely exclude people considered suicidal; therefore, when such behaviour is unexpectedly found, it should not be dismissed. There is unequivocal evidence that antidepressants can increase suicidal behaviour in younger patients,³³ and trigger suicidal behaviours in healthy volunteers³⁴ and hostility in both patients and healthy volunteers.³⁵ Furthermore, those arguing for wider use of antidepressants generally fail to take account of other risks such as sexual dysfunction, pregnancy complications, and falls among older people, and the opportunity costs of unnecessary/ineffective prescribing.

With regard to other claims made by Isacson & Rich:

- Barbui *et al*²⁵ and Guaiana *et al*²⁶ did find inverse correlations between antidepressant use and suicide rates. However, Isacson & Rich ignore the fact that these authors explicitly

rejected a causal interpretation (a point we should have made), noting that decreases in suicide preceded the introduction of SSRIs, an issue previously mentioned by us, but ignored by Isacson & Rich.

- Isacson & Rich seem to have confused Wheeler *et al*'s 2009 international study²⁷ with a 2008 paper, which focused on the UK.³⁰ Our claim that the study refuted a relationship between increased child suicide and decreased prescribing was based on the finding of a ratio of 0.999 between actual suicides and suicides predicted from the linear trends in 10- to 14-year-olds and 15- to 19-year-olds internationally.²⁷ With regard to the newly cited Gibbons *et al*,²⁹ the authors of that study seriously misrepresented the data in their conclusions.³¹
- We agree that introduction of irrelevant covariates in ecological studies might obscure true correlations, but no one advocates using covariates without evidence of relevance, nor did we suggest use of autopsy rates as a covariate. However, it is crucial to control for potential confounding factors such as alcohol consumption; none of Isacson & Rich's cited studies did.
- Isacson & Rich have misinterpreted our point about autopsy rates. Clinical autopsies sometimes detect previously unsuspected suicides, so doing fewer autopsies would likely reduce official suicide rates. Their claim that ill-defined deaths in Sweden have decreased even more than suicides contrasts with Reseland *et al*'s Fig. 1B (p. 80),²² which shows a substantial increase since 1997 with minor yearly fluctuations. Perhaps Isacson & Rich have exploited these fluctuations to suit their argument.

Finally, Isacson & Rich's selected citations are not comprehensive. In fact, they demonstrate the distorted and selective citation practices that muddy the antidepressant/suicide debate and the antidepressant literature more generally. Examples include the following:

- Failing to cite unfavourable studies: Isacson & Rich's claim that only one study failed to demonstrate a decrease in suicide paralleling increased antidepressant use ignores two other negative studies.^{36,37}
- Ignoring unfavourable aspects of a study: Isacson & Rich did not report Barbui *et al*'s conclusion that SSRIs may increase suicidality in adolescents.⁹

In summary, Isacson & Rich selectively ignore evidence of harms, unfavourable results and interpretations, and crucial methodological issues.

Jon Jureidini & Melissa Raven

For: Conclusions

Jureidini & Raven demonstrate impressive scepticism regarding evidence for antidepressants preventing suicide. They dismiss numerous randomised clinical trials plus 50 years of clinical experience demonstrating that antidepressants are effective for treating depression. They dismiss many investigations demonstrating that suicide is mostly a concomitant of depression, and the score of ecological studies demonstrating decreases in suicide paralleling increases in antidepressant use. They produce arguments against individual-based studies showing the same result. Ironically, Jureidini & Raven suspend their sceptic skills regarding possible harms of antidepressants. They find 'unequivocal evidence' that antidepressants can increase 'suicidal behaviour' without acknowledging that this debate is about

suicide, not the more common occurrences of non-fatal suicidal ideation and behaviour. They cite other side-effects of antidepressants which are well known but do not prevent many people with depression from choosing to take them. Nonetheless, Jureidini & Raven recommend doctors would be better 'doing nothing' rather than prescribing antidepressants for depressed and potentially suicidal patients. This position demonstrates a somewhat surprising naivety regarding a classic concept in medical practice, i.e. the risk/benefit ratio.

Jureidini & Raven do not seem concerned that the 'unequivocal evidence' consists of by-products from the randomised controlled trials they have judged inferior with regard to the primary outcome. Nor do they find it problematic that these leftovers consist of unsystematic observations from studies in which most individuals of interest were systematically excluded. If these individuals, judged to be at risk of suicide, had not been excluded, it might have been possible to demonstrate the benefits of antidepressants with regard to suicidal behaviour. Personally, we find this information interesting but not compelling and certainly equivocal at best.

Although Oravec *et al* found no significant correlation between suicide rates and the use of antidepressants between 1985 and 1997 in Slovenia (about 600 suicides annually), their later analysis of 1971–2002 demonstrated that suicide had decreased in Slovenia after a peak during the 1987–1994 period.³⁸ These data have greater statistical power.

The consumption of alcohol was considered in the previously cited studies from Sweden, Hungary and Northern Ireland, and could not explain the decrease in suicide. We are not aware of any significant decrease in alcohol consumption elsewhere that might explain decreases in suicide.

Suicide decreased in Sweden by 8% between 1980 and 1989 before SSRIs were introduced. However, use of pre-SSRI antidepressants in Sweden increased by 46% during the 1980s. Several public health projects aimed at improving the treatment of depression were also going on in the 1980s (e.g. Gotland Project, Defeat Depression, DART). The fact that suicide in many countries started to decrease before SSRIs supports our hypothesis.

We have not exploited minor fluctuations in autopsy rates. In a letter to the Editor,³⁹ we described what we believe are fallacies in the earlier Reseland *et al*²² paper on this topic. A diagram of true Swedish rates of suicides and uncertain deaths is provided in that letter.

We think the most important consideration is to acknowledge what is in front of us. If antidepressants increase the risk of suicide, the more than fivefold increase in their use since 1990 should have led to a suicide catastrophe (cf. thalidomide). However, no such catastrophe has occurred. Instead, we have witnessed a substantial worldwide decrease in suicide. This is the reality that any theory of the effects of antidepressants must address. As we stated in our initial argument, it is not possible to definitively establish that these decreases have been caused by antidepressants. Real-world observations have shown, however, that decreases in suicide in different countries have been proportional to respective increases in the use of antidepressants.⁴⁰ Likewise, individual-based studies have shown that the decrease in suicide has occurred in the part of the population that was treated with antidepressants.¹⁵ We have not heard any convincing alternative explanation of these facts. We find the weight of the evidence makes a strong case for doctors offering their patients with depression treatment with antidepressant medication and saving many of them from suicide instead of 'doing nothing'.

Göran Isacsson & Charles L. Rich

Against: Conclusions

Lacking good evidence that depression causes suicide or that antidepressants make a clinically important difference to depression outcomes, Isacsson & Rich have claimed that increasing antidepressant prescribing decreases suicide. This claim is based primarily on correlations in ecological studies and on individual-based studies with unrepresentative inclusion/ exclusion criteria and equivocal findings. They have also cited a post-mortem toxicology study that ignores withdrawal, which has been linked to suicidality,⁴¹ assumes that only people with detectable antidepressant levels have been exposed, and uses an unrepresentative control group.

Ioannidis has demonstrated how the myth of antidepressant effectiveness is supported by small, biased randomised trials with clinically irrelevant outcomes and selective and distorted reporting and interpretation.⁴² We have endeavoured to show how Isacsson & Rich are key proponents of a similar myth that antidepressants reduce suicide rates. Greenberg has outlined how distorting citations can generate 'information cascades' (bandwagons) that give 'unfounded authority' to claims.⁴³ We have highlighted multiple examples of Isacsson & Rich's use of citation bias and 'citation diversion' (misrepresentation of findings) to give unfounded authority to their claims. Far from 'dismissing' studies, we have critically analysed whether their methodology and findings support Isacsson & Rich's interpretations. Mostly they do not, but Isacsson & Rich have ignored many of our specific criticisms and misunderstood others.

Isacsson & Rich continue to confuse autopsy rates and ill-defined death rates; we mentioned fluctuations in the latter, not the former. They argue that a diagram plotting suicides and 'uncertain cases' (an undefined term from an unstated data source) supports their claim that ill-defined deaths have decreased more than suicides in Sweden; it actually shows the opposite. There are other factual inaccuracies: the Defeat Depression Campaign ran in the 1990s,⁴⁴ not the 1980s, and alcohol was not considered in the previously cited Hungarian study.⁵

Isacsson & Rich seem unaware of normal assessment of candidate covariates in multivariate analyses. Furthermore, they imply that if alcohol consumption was a confounder, it should explain suicide trends. Having settled on depression as a single dominant cause of suicide and antidepressants as a single dominant solution, they argue that critics should similarly suggest a single alternative cause and solution.

Isacsson & Rich, who accuse us of naivety, seem unaware that the opposite of benefit is harm, and that risk/benefit ratios are inherently flawed.⁴⁵ Becoming suicidal while taking antidepressants is a serious harm, whether or not there is increased risk of completed suicide. They suggest that including individuals who are suicidal in trials might reveal benefits of antidepressants, but ignore the possibility that it might expose harms. We do share their concern that evidence of suicidal behaviour comes from unsystematic observations; evidence would be stronger if trials were not biased against detection of harms.⁴⁵

Isacsson & Rich close by distorting our comment that 'doing nothing is better than doing something useless or harmful', accusing us of advocating 'doing nothing' for people with depression. They 'wish to do something to prevent suicide'. So do we. Were it the topic of this debate, we could elaborate on public health interventions. Regardless of alternatives, the injunction to 'first do no harm' requires that we not prescribe potentially harmful antidepressants based on wishful thinking. The idea that there is a single cause and a simple solution to the tragic reality of suicide is enormously appealing, and misinformed.

Jon Jureidini & Melissa Raven

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