Antidepressants and suicide in young people

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ABSTRACT

- A number of recent studies have allayed fears about antidepressants precipitating suicidal behaviour in young people. Indeed, antidepressants appear to be conspicuous by their absence of use in young people who die by suicide.
- Furthermore, there is concern that the reduced prescribing of antidepressants to young people may be associated with an increase in youth suicide in the United States.
- Although not first-line treatment, antidepressants should not be denied young people if psychosocial and cognitive behavioural therapies are not effective for major depression.

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The recent article[1] "Evaluating medicines: let's use *all* the evidence" was a timely reminder of the potential limitations of relying solely on randomised clinical trials (RCTs) in making decisions about the use of medications.

Nowhere is this more applicable than in the contentious area of antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), and potential suicide risk in children and adolescents.[2] There have been sporadic case reports of an association between antidepressants and suicidal behaviour;[3] the efficacy of antidepressants in young people has been questioned;[4] and meta-analyses of RCTs of antidepressants have demonstrated a weak association with suicidal behaviour, although not with suicide.[2,5,6]

Although the RCT is the recognised "gold standard", certain questions cannot be answered by such trials. With regard to suicide, this is partly because of the ethical dilemma of offering placebo to people who may be suicidal, but, even more so, is the impossibility of mounting a sufficiently powered study because of the low base rate of suicide. For example, it has been calculated that, if one were to use the RCTs of antidepressants which have been published, then it would have been necessary to have recruited about 1.9 million subjects to detect a 20% decrease in suicide.[7] It is also pertinent that, in the RCTs which have led to concerns, suicidal behaviours had not been the specific focus of research, but were spontaneously reported events,[8] and it could be argued that an overdose of active medication would be more likely to evoke reporting than an overdose of placebo.

Because of limitations in the interpretation of RCTs, it has been observed that real-life clinical monitoring may be the only way in which clinicians and drug regulators can make reasoned decisions about some treatments. Indeed, with regard to antidepressants and suicide in young people, there have been a number of recent naturalistic observations published, and it is important to incorporate them into clinical decision making.

Ludwig and Marcotte analysed SSRI use and suicide data from 27 countries, and found a strong association between an increase in antidepressant prescribing and a reduction of suicide in people older than 15 years,[9] although the data were not conclusive for people aged 10–15 years. However, there have been studies from four countries which can inform us further about suicide and antidepressants in the young.

Jick et al analysed data from the United Kingdom General Practice Research Database (GPRD), which contains more than 35 million patient-years of information. They found a similar risk of suicide when commencing one of either two tricyclic antidepressants or two SSRI antidepressants, and a decreasing risk with time.[10] An accompanying editorial noted that the analysis simply demonstrated that antidepressants were being "prescribed for the right indication, and that they do not immediately eliminate suicide risk. That we knew".[11] It is important to note that Jick et al extended their analysis to examine adolescent suicide,[10] and found no suicides in those aged 10–19 years who were on one or other of the study drugs. However, they reported that there were 15 people in that age group in the GPRD who had died by suicide, and none had received an antidepressant drug. One might, perhaps provocatively, ask why the media did not criticise practitioners for not using antidepressants in those people.

That the data analysed by Jick et al were not simply an artefact of British practice has been demonstrated by subsequent reports from three other countries. In Sweden, Isacsson et al reported a toxicological study of more than 14 000 suicides between 1992 and 2000 and compared them with control subjects.[12] They found that SSRIs were under-represented compared with other antidepressants in people who died by suicide (odds ratio, 0.83; 99% CI, 0.77–0.90). They also addressed the issue of suicide in younger people, and found in the 15–19 years age group that SSRIs had a lower relative risk (RR, 0.14; 95% CI, 0.05–0.43) for suicide compared with non-SSRI antidepressants. In people younger than 15 years, there were 52 suicides and no SSRIs were found by toxicological screening, although other antidepressants were detected in seven of these people. A study from the United States provided even more striking results — Moskos et al reported that, in a series of 49 suicides aged 13–21 years, "not one demonstrated therapeutic or subtherapeutic levels of psychotropic medications upon autopsy".[13] More recently, Søndergård et al, in a pharmacoepidemiological study of youth suicide in Denmark between 1995 and 1999, found that none of 42 suicides aged 10–17 years had been treated with SSRIs in the 2 weeks before their deaths, and none of the 37 boys who died by suicide had ever been treated with antidepressants at any time during the study period.[14] However, there is one other US study in which one of 36 suicides under the age of 18 years had both sertraline and bupropion detected by toxicological analysis, and the authors noted that "the detection of antidepressants at autopsy was quite rare".[15]

With other research indicating that two-thirds of young suicides had significant mood disorders,[16] it would not have been unexpected for more young people in these five studies to have recently been prescribed antidepressants before their suicide. Indeed, for only one out of 194 young suicides to have had evidence of antidepressant use is quite remarkable, and totally incongruent with the assertion that SSRI antidepressants may precipitate suicide in the young.

No antidepressant has yet been approved for use in major depression in children and adolescents in Australia, and fluoxetine

is the only antidepressant so approved in the UK and the US. However, it is of interest to reflect that the SSRIs fluvoxamine and sertraline are approved for use in obsessive compulsive disorder (OCD) in children and adolescents in Australia, and there have not been reports of suicide with the use of those antidepressants in young people with OCD — yet another piece of collateral evidence (again, not from an RCT) which lends confidence to the use of SSRI antidepressants in young people.

This viewpoint should not be interpreted as promoting uncritically the use of antidepressants in young people. Antidepressants are not necessarily first-line treatment, and they should be used only as an adjunct to psychosocial and cognitive behavioural therapies, and after consultation with the patient and family. However, these recent studies add considerable weight to the previous cautious endorsement by Rey and Dudley of the appropriate use of antidepressants in young people.[17]

In view of this recent research, it is not unexpected that concern has been expressed in the US that, in 2004, for the first time in a decade, the previously declining suicide rate in young people increased.[18,19] This coincided with a reduction in antidepressant prescribing, which was almost certainly brought about by initial fears that have since been allayed by these recent studies. Indeed, it is not unexpected that Bridge et al recently concluded that the "Benefits of antidepressants appear to be much greater than risks from suicidal ideation/suicide attempt across indications".[2]

Competing interests

Robert Goldney has received honoraria, travel grants and research support from a number of pharmaceutical companies.

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