Suicide, depression, and antidepressants
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Suicide, depression, and antidepressants

Patients and clinicians need to balance benefits and harms

Unipolar depression, one of the most important causes of disability worldwide, is characterised by depressed mood, hopelessness, helplessness, intense feelings of guilt, sadness, low self-esteem, thoughts of self-harm, and suicide. Up to 15% of patients with unipolar depression eventually commit suicide. Although clinical guidelines recommend treating moderate to severe depression with antidepressant drugs, debate persists on whether some antidepressant drugs, in particular the selective serotonin reuptake inhibitors (SSRIs), cause the emergence or worsening of suicidal ideas in vulnerable patients. New insights on this key issue have been provided by three articles published in this issue.

Fergusson et al conducted a systematic review of published randomised controlled trials comparing SSRIs with either placebo or other active treatments in patients with depression and other clinical conditions. They found an almost twofold increase in the odds of fatal and non-fatal suicidal attempts in users of SSRIs compared with users of placebo or other therapeutic interventions (excluding tricyclics). No increase in risk was seen, however, when only suicidal attempts were compared between SSRIs and placebo. Finally, no differences were observed when overall suicide attempts were compared between users of SSRIs and tricyclic antidepressants.

By contrast, Gunnell et al included in their review both published and unpublished randomised controlled trials submitted by pharmaceutical companies to the safety review of the Medicine and Healthcare products Regulatory Agency. These trials compared SSRIs with placebo in adults with depression and other clinical conditions. Three outcome measures were studied: completed suicide, non-fatal self harm, and suicidal thoughts. The researchers found no evidence for an increased risk of completed suicide, only weak evidence of an increased risk of self-harm, and inconclusive evidence of an increased risk of suicidal thoughts (estimates compatible with a modest protective or adverse effect).

Finally, the nested case-control study reported by Martinez et al, based on information extracted from the General Practice Research Database, analysed the risk of non-fatal self harm and suicide in patients with a new diagnosis of depression who were prescribed SSRIs or tricyclics. The cohort included 146,095 patients. In comparison with users of tricyclics, users of SSRIs were not at increased risk of suicide or non-fatal self harm. However, in patients aged 18 or less, weak evidence indicated a higher risk of non-fatal self harm in those prescribed SSRIs.

From a methodological viewpoint, these articles highlight the relevance of combining randomised with observational evidence, taking into account the limitations of both approaches. Randomised controlled trials included selected patient populations followed up for short periods of time; these studies were not designed to identify completed or attempted suicides specifically, and reported data on this outcome variable only in a subgroup of studies. Additionally, given that a diagnosis of unipolar depression was not required for inclusion in the review, trials with different patient populations were included. Although the procedure of pooling data from hundreds of trials increased the overall numbers, absolute numbers of patients attempting and committing suicide remained very low, leaving the possibility that reporting or not reporting a few cases could have completely changed the overall outcome. Conversely, the study by Martinez et al analysed a large number of newly depressed patients. However, the lack of randomisation raises the problem of confounding by indication because doctors might preferentially prescribe SSRIs on safety grounds in patients at risk of suicide. Although authors adjusted statistically for this potential confounder, the possibility that other known or unknown variables might have acted in unpredictable ways cannot be ruled out.

Taking into account these limitations, we can get some useful insights for clinical practice. Firstly, current evidence that indicates no clear relation between SSRIs and suicide, together with available robust evidence of efficacy of treatment with antidepressant drugs in the pharmacological management of moderate to severe unipolar depression, should encourage doctors to prescribe effective doses of these drugs in such patients. Doctors should additionally be aware that SSRIs, similarly to tricyclics, may induce or worsen suicidal ideation and suicide attempts during the early phases of treatment, possibly because they cause agitation and activation particularly at that time. During these early phases, doctors should plan frequent follow up visits and also consider a possible supporting role for family members and caregivers. Patients should be advised against withdrawing treatment abruptly, given the risk of reactions to discontinuation. Secondly, the strongest evidence applies to moderate to severe depression only and therefore cannot be extrapolated to mild depression. Thirdly, these indications apply to adults only, whereas in children and adolescents the balance...
between benefits and harms seems to be negative, with little evidence of efficacy and increasing evidence of an association between exposure to SSRIs and other antidepressant drugs and emergence of suicidal thought and behaviours.1-11 This risk, in addition to the lack of data on the long term implications of exposing a developing brain to antidepressant drugs, should discourage the routine prescribing of antidepressant drugs in children and adolescents.

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Competing interests: JG has received research funding and support from Sanofi-Aventis and GlaxoSmithKline and is currently in discussion with several other companies that manufacture SSRIs about collaboration on planned independent trials and systematic reviews.


