Perspectives

The downsides of antidepressants

Health reporter Ray Moynihan explores disturbing new data about the ever-popular pills

After analysing antidepressant use among older people in Britain for more than a decade, a team of researchers has come up with some alarming new findings. Released recently, their study barely raised a murmur in Australia, but its implications are potentially enormous.[1] If the new data are to be believed, for older people, the most commonly prescribed drugs for depression may be associated with an *increased* risk of serious health problems and death compared with less common antidepressants or none at all.

Conducted as part of the Health Technology Assessment program, this British prospective cohort study investigated the risks associated with antidepressants being used by people aged 65 years or older during the decade or so to 2008. Its database included more than 60 000 people from 570 general practices across the United Kingdom who had been newly diagnosed with depression.

Results published in the *BMJ* show that more than half of the antidepressant prescriptions issued to this group were for drugs from the selective serotonin reuptake inhibitor (SSRI) class, almost a third were for older tricyclics, and just over one in 10 were for other antidepressants.[1] Eleven per cent of the people in the study did not take any drugs for depression. For those who did take antidepressants, the median duration of use was 1 year. Interestingly, more than two-thirds of the older people had the severity of their depression classified as mild, a quarter as moderate, and just under 5% as severe — and these proportions were similar for those who were and those who were not prescribed antidepressants.

The researchers then compared the adverse events experienced by people during the time they were taking the drugs with those experienced by people during periods when they weren't taking the drugs, and it was these comparisons that produced the unexpected and disturbing associations.

The absolute risk of death from all causes over 1 year was 10.6% for patients taking SSRIs, 8.1% for those taking tricyclics, 11.4% for those taking other antidepressants, and 7.0% for people not taking any antidepressants. Moreover, those taking antidepressants suffered a significantly greater number of serious adverse events:

> All classes of antidepressant drug were associated with significantly increased risks of all cause mortality, attempted suicide/self harm, falls, fractures, and upper gastrointestinal bleeding compared with when these drugs were not being used.[1]

> "All classes of antidepressant drug were associated with significantly increased risks of all cause mortality"

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Despite being heavily promoted as better than the older medicines, the study found that, compared with tricyclic antidepressants, the newer SSRI class "may be associated with an increased risk of ... all cause mortality, stroke/transient ischaemic attack, falls, fracture, epilepsy/seizures, and hyponatraemia".

The obvious limitation here is that the study was observational, rather than a randomised controlled trial. However, as is made clear in their full 200-page report for the Health Technology Assessment program,[2] the researchers went to great lengths to identify a wide range of potentially confounding variables, including age, sex, comorbidities and the severity of depression.

Yet after adjusting the results for the confounding variables, key associations were largely unaffected. For example, after adjusting for confounders, taking SSRIs was still associated with a roughly 50% higher chance of death in relative terms, as well as an increased risk of serious adverse events including attempted suicide, falls and fractures, compared with those diagnosed with depression who were not taking antidepressants.

In discussing the findings of their observational study, the authors highlight the difficulty of untangling the effect of the drugs from the effect of the underlying condition, particularly as they were unable to adjust for the way the severity of a patient's depression might have changed during the decade of the study. Putting their results in the context of other data, the researchers conclude that their findings of higher rates of attempted suicide for all classes of antidepressants "suggest an effect of depression itself rather than a direct causal effect" of the drugs.[2] By contrast, they conclude their findings of higher rates of falls, fractures and hyponatraemia associated with some antidepressants are generally in line with existing data.

Importantly, the study's limitation is also its strength. Looking at the serious health problems experienced by many thousands of people taking antidepressants over a long period, these real-world results are potentially more relevant than small, short-term, company-funded trials with extensive exclusion criteria, which may lead to overstating benefits and playing down harms of drugs. Whatever your view of the benefits of these heavily marketed medicines, this latest study provides important new information about their associated downsides.

Competing interests: No relevant disclosures.

Provenance: Commissioned; not externally peer reviewed.

1 Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011; 343: d4551. doi: 10.1136/bmj.d4551.

2 Coupland CAC, Dhiman P, Barton G, et al. A study of the safety and harms of antidepressant drugs for older people: a cohort study using a large primary care database. *Health Technol Assess* 2011; 15 (28). http://www.hta.ac.uk/fullmono/mon1528.pdf (accessed Sep 2011).