Most antidepressant drugs ineffective for children and teens, according to study

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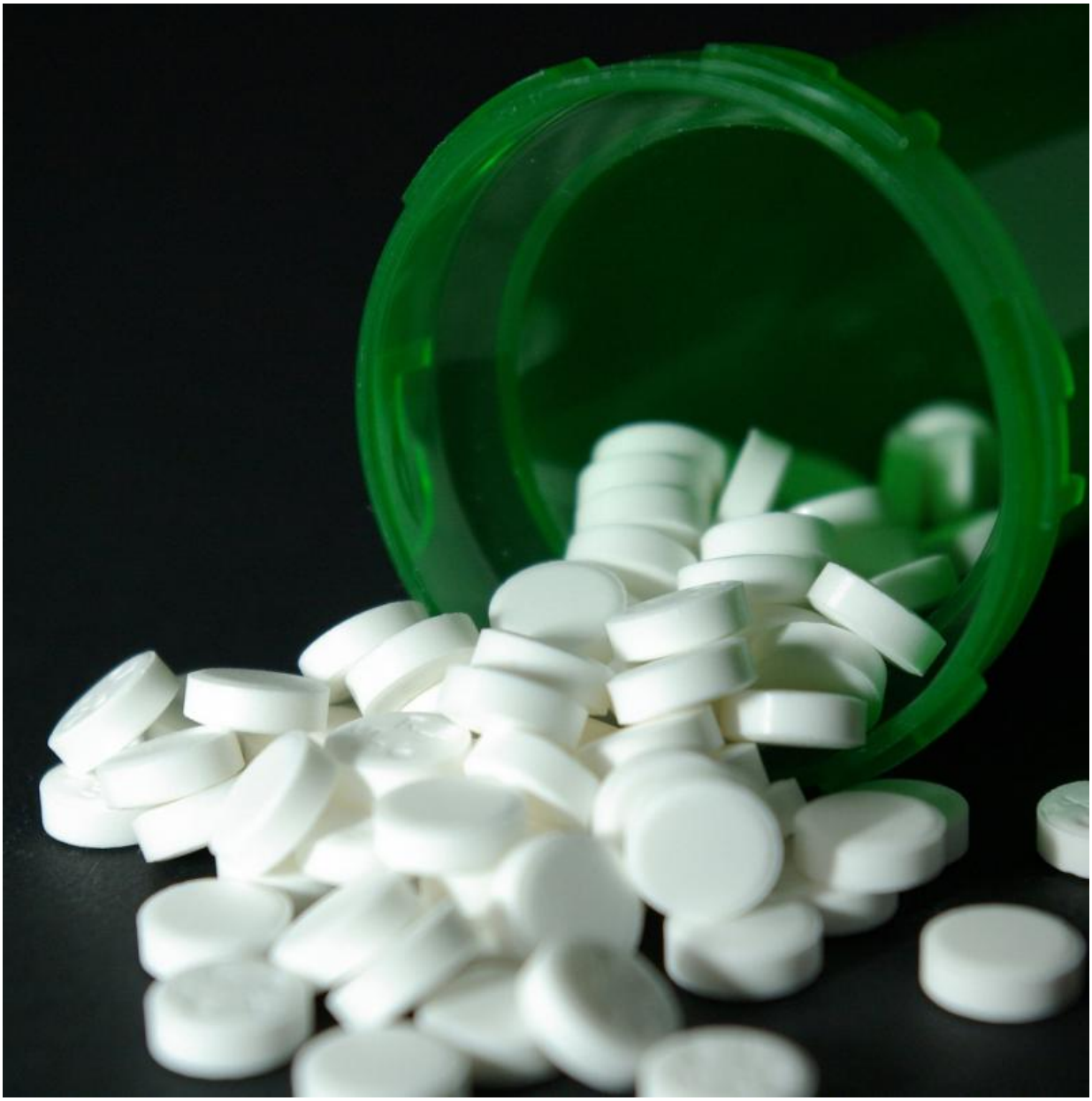

Pills. Credit: Public Domain

Most available antidepressants are ineffective, and some may be unsafe, for children and teenagers with major depression, according to the most comprehensive comparison of commonly prescribed antidepressant drugs so far, published in *The Lancet*.

The findings indicate that out of 14 antidepressant drugs, only fluoxetine was more effective at relieving the symptoms of depression than placebo, whilst taking venlafaxine was linked with an increased risk of engaging in suicidal thoughts and attempts compared with placebo and five other antidepressants.

However, the true effectiveness and risk of serious harms such as suicidal thoughts and attempts remains unclear because of the small number and poor design of clinical trials assessing these antidepressants, and the selective reporting of findings in published trials and clinical study reports, caution the authors.

"The balance of risks and benefits of antidepressants for the treatment of major depression does not seem to offer a clear advantage in children and teenagers, with probably only the exception of fluoxetine. We recommend that children and adolescents taking antidepressants should be monitored closely, regardless of the antidepressant chosen, particularly at the beginning of treatment," explains co-author Professor Peng Xie from The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

"Without access to individual-level data it is difficult to get accurate effect estimates and we can't be completely confident about the accuracy

of the information contained in published and unpublished trials. It has been widely argued that there needs to be a transformation of existing scientific culture to one where responsible data sharing should be the norm," says lead author Dr Andrea Cipriani at the University of Oxford in the UK. "Hundreds of thousands of people worldwide have agreed to participate in trials aiming to find better treatments for their disorders and, ultimately, help the progress of medical science. Patients' privacy must be guaranteed by adequate policies and technological measures, but delay in implementing responsible data sharing policies has negative consequences for medical research and patient outcomes, as demonstrated by this study. Access to raw clinical trial data provides the unique opportunity not only for validation and replication of results but also the in-depth study of specific factors that may affect treatment outcome at the individual patient level."

Major depressive disorder is common in children and adolescents, affecting around 3% of children aged 6 to 12 years and about 6% of teenagers aged 13 to 18 years. Psychological treatments are recommended as the first-line treatment for depression in many clinical guidelines, and in 2004 the US Food and Drug Administration (FDA) black box warning against the use of antidepressants in young people up to 24 years because of concern about increased risk of suicidality. However, use of antidepressants has slowly increased between 2005 and 2012. For example, the proportion of US children and teenagers (aged 0-19 years) taking antidepressants increased from 1.3% to 1.6%, and in the UK from 0.7% to 1.1%. Sertraline is the most widely prescribed antidepressant in the USA and fluoxetine is the most common in the UK.

Cipriani and colleagues did a systematic review and network meta-analysis of all published and unpublished randomised trials comparing the effects of 14 antidepressants in young people with major depression up to the end of May 2015. They ranked antidepressants by efficacy (change in depressive symptoms and response to treatment), tolerability

(discontinuation due to adverse events), acceptability (discontinuation due to any cause), and associated serious harms (ie, suicidal thoughts and attempts). They took into account the quality of included studies (Cochrane risk of bias) and also assessed the overall quality of the retrieved evidence (GRADE).

Analysis of 34 trials involving 5260 participants (average age 9 to 18 years) showed that the benefits outweighed the risks in terms of efficacy and tolerability only for fluoxetine (figure 3). Nortriptyline was less efficacious than seven other antidepressants and placebo. Imipramine, venlafaxine, and duloxetine had the worst profile of tolerability, leading to significantly more discontinuations than placebo. Venlafaxine was linked with an increased risk of engaging in suicidal thoughts or attempts compared with placebo and five other antidepressants (figure 4). The authors warn that due to the lack of reliable data, it was not possible to comprehensively assess the risk of suicidality for all drugs.

22 (65%) trials were funded by pharmaceutical companies. Ten (29%) trials were rated as high risk of bias, 20 (59%) as moderate, and four (12%) as low (appendix pages 18-21).

Overall quality of evidence for primary outcomes was rated as very low for most comparisons, which restricts the implications of the results for clinical practice (appendix pages 77-86).

Writing in a linked Comment, Dr Jon Jureidini at the University of Adelaide in Australia questions how many more suicidal events might have been revealed had individual patient-data been available. He points out, "[For example], in four trials of paroxetine versus placebo, only 13 (3%) of 413 events were reported in the paroxetine group; this seems implausible when individual patient-level data reanalysis of just one of those studies found ten events in only 93 patients given paroxetine (10.8%)."

He adds, "The effect of misreporting is that antidepressants, possibly including fluoxetine, are likely to be more dangerous and less effective treatments than has been previously recognised, so there is little reason to think that any antidepressant is better than nothing for young people...Patients who take part in randomised controlled trials have a right to expect that maximum benefit will come from the data they generate. We doctors and researchers are failing to meet our obligation to research participants and to our patients, and we will only succeed if independent researchers such as Cipriani and colleagues are able to analyse individual patient-level data. Claims that appropriate access to such data is incompatible with intellectual property constraints and patient privacy must be strongly resisted."

More information: Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis, dx.doi.org/10.1016/S0140-6736(16)30385-3, www.thelancet.com/journals/lan … (16)30385-3/abstract

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