

Review: antidepressants associated with increased risk of suicidality in adults aged less than 25 years

QUESTION

Question: What is the risk of suicidal behaviour within clinical trials of antidepressants in adults?

Outcomes: Primary outcome: definitive suicidal behaviour or ideation (completed suicide, attempted suicide or preparatory acts), secondary outcome: suicidal behaviour (preparatory actions).

METHODS

Design: Systematic review with meta-analysis.

Data sources: Data requested from 8 industry sponsors of 12 marketed antidepressant products were used. FDA-specified data formats provided instructions for identifying and classifying events possibly related to suicidality and how events would be classified. The search date was not reported, and the majority of trials were unpublished.

Study selection and analysis: Double-blind randomised placebo-controlled trials assessed the use of one of the 12 antidepressants in adults for any indication of suicidality. The antidepressants were bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluoxetine/olanzapine (ultimately excluded from the analysis), fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline and venlafaxine. A total of 372 trials (n=99 231) were included in the dataset. Trials limited to known drug responders, those with fewer than 20 participants, studies not providing patient level data and studies with non-antidepressant active control were excluded. Individual patient-level data were analysed using a conditional logistic regression model. Heterogeneity between studies was assessed.

MAIN RESULTS

There were a total of 8 (0.01%) completed suicides, 134 (0.14%) attempted suicides and 378 (0.38%) people experiencing ideation alone. Overall, there was no increased risk of suicidality (ideation or worse) with active treatment versus placebo (OR 0.85, 95% CI 0.71 to 1.02; p=0.08). Ideation or worse was rare in participants

with non-psychiatric indications (12 out of 13284). Risk of ideation or worse was reduced in participants with any psychiatric indication, but this was of borderline significance (OR 0.83, 95% CI 0.69 to 1.00; p=0.05). Suicide behavioural risk (completed suicide, attempted suicide or preparatory acts) was associated with age; participants aged <25 years had increased risk of suicidal behaviour with active treatment versus placebo, OR 2.30, 95% CI 1.04 to 5.09. Treatment was associated with a reduced risk of suicidal behaviour in the age group of 25 to 64 years, but this was not significant (OR 0.87, 95% CI 0.58 to 1.29). Participants aged ≥65 years showed a reduced risk of suicidal behaviour with active drug treatment (OR 0.06, 95% CI 0.01 to 0.58). When suicidal behaviour was grouped with ideation the age <25 years group showed a non-significant trend towards increased risk with active treatments (OR 1.62, 95% CI 0.97 to 2.71), whereas both the 25 to 64 years age group and the group of persons aged ≥65 years showed a reduced risk (OR 0.79, 95% CI 0.64 to 0.98; OR 0.37, 95% CI 0.18 to 0.76 respectively). When age was modelled as a continuous variable, the OR for suicidal behaviour or ideation declined at a rate of 2.6% per year of age (-3.9% to -1.3% p=0.0001) and the OR for suicidal behaviour declined at a rate of 4.6% per year of age (-7.4% to -1.8% p=0.001).

CONCLUSIONS

The evidence suggests that there is an increased risk of suicidal behaviour in adults aged <25 years who receive antidepressants. Those aged ≥25 years have no increased or decreased risk (in people aged 65 years or older).

ABSTRACTED FROM

Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* 2009;**339**:b2880.

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It has been known for a long time that antidepressants can increase the risk of suicidal thoughts and behaviour.¹ Stone and colleagues have conducted a re-analysis of FDA data of 372 randomised placebo-controlled efficacy trials conducted not only in the indication of major depressive disorder but also in all other psychiatric and non-psychiatric indications. Main results indicated that the risk for suicidal behaviour in patients aged <25 years taking antidepressants as compared to placebo was significantly elevated, neutral in patients aged 25 to 64 years and protective for those aged ≥65 years. The second result was the strong age-relatedness of suicidal behaviour. On the basis of these two main results, the FDA ordered that for all antidepressants the existing black-box warning should be updated to include warnings about suicidality of young adults. However, such warnings may discourage psychiatrists from using antidepressants, which in turn might increase suicidality.

Gibbons² showed that after the release of the FDA warnings the antidepressant prescription rates decreased in the USA and the Netherlands, by about 22%. Simultaneously, the suicide rates in youths increased up to 49% in the Netherlands and up to 14% in the USA.

This raises the question whether these findings really justify such a drastic step. There is, beyond doubt, a strong age-relatedness, but the increased risk for suicidal behaviour in young adults aged <25 years alone is only just statistically significant. The second main finding, of the age-relatedness of suicidal behaviour, is strongly dependent on the robust suicide protective effect in higher ages, which per se also does not necessarily suggest a suicide warning that has general effects on overall antidepressant prescription rates.

The discovery of age as an influential variable of antidepressant-induced suicidal behaviour significantly adds to our knowledge, opens new research

fields and suggests closer suicidality monitoring in clinical daily routine. However, though the paper by Stone and colleagues is a landmark in suicide research, the consequential FDA black-box warnings may not have been fully justified.

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Competing interests: None.

1. **Möller HJ.** Is there evidence for negative effects of antidepressants on suicidality in depressive patients? A systematic review. *Eur Arch Psychiatry Clin Neurosci* 2006;**256**:476-96.
2. **Gibbons RD, Brown CH, Hur K, et al.** Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 2007;**164**:1356-63.

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