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# [Intervention Review]

# Antidepressants versus placebo for panic disorder in adults

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Editorial group: Cochrane Common Mental Disorders Group. Publication status and date: New, published in Issue 4, 2018.

**Citation:** Bighelli I, Castellazzi M, Cipriani A, Girlanda F, Guaiana G, Koesters M, Turrini G, Furukawa TA, Barbui C. Antidepressants versus placebo for panic disorder in adults. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No.: CD010676. DOI: 10.1002/14651858.CD010676.pub2.

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# ABSTRACT

# Background

Panic disorder is characterised by repeated, unexpected panic attacks, which represent a discrete period of fear or anxiety that has a rapid onset, reaches a peak within 10 minutes, and in which at least four of 13 characteristic symptoms are experienced, including racing heart, chest pain, sweating, shaking, dizziness, flushing, stomach churning, faintness and breathlessness. It is common in the general population with a lifetime prevalence of 1% to 4%. The treatment of panic disorder includes psychological and pharmacological interventions. Amongst pharmacological agents, the National Institute for Health and Care Excellence (NICE) and the British Association for Psychopharmacology consider antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), as the first-line treatment for panic disorder, due to their more favourable adverse effect profile over monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Several classes of antidepressants have been studied and compared, but it is still unclear which antidepressants have a more or less favourable profile in terms of effectiveness and acceptability in the treatment of this condition.

# Objectives

To assess the effects of antidepressants for panic disorder in adults, specifically:

1. to determine the efficacy of antidepressants in alleviating symptoms of panic disorder, with or without agoraphobia, in comparison to placebo;

2. to review the acceptability of antidepressants in panic disorder, with or without agoraphobia, in comparison with placebo; and

3. to investigate the adverse effects of antidepressants in panic disorder, with or without agoraphobia, including the general prevalence of adverse effects, compared to placebo.

#### Search methods

We searched the Cochrane Common Mental Disorders' (CCMD) Specialised Register, and CENTRAL, MEDLINE, EMBASE and PsycINFO up to May 2017. We handsearched reference lists of relevant papers and previous systematic reviews.

# **Selection criteria**

All double-blind, randomised, controlled trials (RCTs) allocating adults with panic disorder to antidepressants or placebo.

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#### Data collection and analysis

Two review authors independently checked eligibility and extracted data using a standard form. We entered data into Review Manager 5 using a double-check procedure. Information extracted included study characteristics, participant characteristics, intervention details and settings. Primary outcomes included failure to respond, measured by a range of response scales, and treatment acceptability, measured by total number of dropouts for any reason. Secondary outcomes included failure to remit, panic symptom scales, frequency of panic attacks, agoraphobia, general anxiety, depression, social functioning, quality of life and patient satisfaction, measured by various scales as defined in individual studies. We used GRADE to assess the quality of the evidence for each outcome

#### **Main results**

Forty-one unique RCTs including 9377 participants overall, of whom we included 8252 in the 49 placebo-controlled arms of interest (antidepressant as monotherapy and placebo alone) in this review. The majority of studies were of moderate to low quality due to inconsistency, imprecision and unclear risk of selection and performance bias.

We found low-quality evidence that revealed a benefit for antidepressants as a group in comparison with placebo in terms of efficacy measured as failure to respond (risk ratio (RR) 0.72, 95% confidence interval (CI) 0.66 to 0.79; participants = 6500; studies = 30). The magnitude of effect corresponds to a number needed to treat for an additional beneficial outcome (NNTB) of 7 (95% CI 6 to 9): that means seven people would need to be treated with antidepressants in order for one to benefit. We observed the same finding when classes of antidepressants were compared with placebo.

Moderate-quality evidence suggested a benefit for antidepressants compared to placebo when looking at number of dropouts due to any cause (RR 0.88, 95% CI 0.81 to 0.97; participants = 7850; studies = 30). The magnitude of effect corresponds to a NNTB of 27 (95% CI 17 to 105); treating 27 people will result in one person fewer dropping out. Considering antidepressant classes, TCAs showed a benefit over placebo, while for SSRIs and serotonin-norepinephrine reuptake inhibitor (SNRIs) we observed no difference.

When looking at dropouts due to adverse effects, which can be considered as a measure of tolerability, we found moderate-quality evidence showing that antidepressants as a whole are less well tolerated than placebo. In particular, TCAs and SSRIs produced more dropouts due to adverse effects in comparison with placebo, while the confidence interval for SNRI, noradrenergic reuptake inhibitors (NRI) and other antidepressants were wide and included the possibility of no difference.

#### Authors' conclusions

The identified studies comprehensively address the objectives of the present review.

Based on these results, antidepressants may be more effective than placebo in treating panic disorder. Efficacy can be quantified as a NNTB of 7, implying that seven people need to be treated with antidepressants in order for one to benefit. Antidepressants may also have benefit in comparison with placebo in terms of number of dropouts, but a less favourable profile in terms of dropout due to adverse effects. However, the tolerability profile varied between different classes of antidepressants.

The choice of whether antidepressants should be prescribed in clinical practice cannot be made on the basis of this review.

Limitations in results include funding of some studies by pharmaceutical companies, and only assessing short-term outcomes.

Data from the present review will be included in a network meta-analysis of psychopharmacological treatment in panic disorder, which will hopefully provide further useful information on this issue.

# PLAIN LANGUAGE SUMMARY

#### Antidepressants for panic disorder in adults

#### Why is this review important?

Panic disorder is common in the general population. It is characterised by panic attacks, periods of fear or anxiety with a rapid onset in which other characteristic symptoms are experienced (involving bodily systems and fearful thoughts). The treatment of panic disorder includes psychological and pharmacological interventions, often used in combination. Among pharmacological interventions, the standard treatment suggested by guidelines is different classes of antidepressants. Evidence for their effectiveness and acceptability is unclear.

#### Who will be interested in this review?

People with panic disorder and general practitioners.

#### What questions does this review aim to answer?

How effective are antidepressants compared to a sham treatment (known as placebo) in treating panic disorder?

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What is the acceptability of antidepressants compared to placebo in treating panic disorder?

How many unintended and untoward effects (adverse effects) do antidepressants have compared to placebo in people with panic disorder?

#### Which studies were included in the review?

We searched electronic databases to find all relevant studies. The medical studies included in the review compared treatment with antidepressants or placebo in adults with a diagnosis of panic disorder. The studies also had to be randomised controlled trials (RCTs), which means adults were allocated at random (by chance alone) to receive the treatment or placebo. We included 41 RCTs for a total of 9377 people in the review.

# What does the evidence from the review tell us?

We found evidence showing that antidepressants are better than placebo in terms of effectiveness and number of people leaving the study early. However, our findings also showed that antidepressants are less well tolerated than placebo, producing more dropouts due to adverse effects. Results are limited in the following ways: some studies were funded by pharmaceutical companies, and only short-term outcomes were assessed. We found almost no data on other clinically relevant outcomes, such as functioning and quality of life. The quality of the available evidence ranged from very low to high.

#### What should happen next?

Studies with outcomes assessed at longer-term follow-up visits should be carried out to establish whether the effect is transient or maintained. Trials should better report any harms experienced by participants during the trial. In addition, a further analysis with an approach called 'network meta-analysis' will include all psychopharmacological treatments available for panic disorder, and will likely shed further light on this compelling issue, also being able to provide more information with regard to comparative efficacy of different available interventions.