



## Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: November 2018

### **Depression: the efficacy and acceptability of antidepressants in the acute management of depression**

A large systematic review and network meta-analysis of 522 double-blind placebo-controlled and head-to-head randomised controlled trials found few differences overall between antidepressants for the initial treatment of acute major depressive disorder. The median duration of acute treatment was 8 weeks. The evidence supports choosing an antidepressant on an individual basis, with selective serotonin reuptake inhibitors as first choice given their favourable balance of benefits and harms. This approach is in line with the NICE guidelines on [depression in adults](#) (being [updated](#)) and [depression in adults with a chronic physical health problem](#), and the NICE quality standard on [depression in adults](#).

#### **Overview and current advice**

Depression is a broad and heterogeneous diagnosis. Central to it is depressed mood and/or loss of pleasure in most activities. Severity of the disorder is determined by both the number and severity of symptoms, as well as the degree of functional impairment. A formal diagnosis using the ICD-10 classification system requires at least 4 out of 10 depressive symptoms, whereas the DSM-IV system needs at least 5 out of 9 for a diagnosis of major depression. Symptoms should be present for at least 2 weeks and each symptom should be present at sufficient severity for most of every day. DSM-IV needs at least 1 and ICD-10 at least 2 of the key symptoms (low mood, loss of interest and pleasure or loss of energy) to be present.

The NICE guidelines on [depression in adults](#) (being [updated](#)) and [depression in adults with a chronic physical health problem](#) support a stepwise approach in treating depression based on the needs the person has and the severity of symptoms. Low intensity psychosocial interventions, such as computerised cognitive behavioural therapy, are recommended as first-line treatments for mild to moderate depression (based on the person's preference). Antidepressants are reserved as an option for when non-drug interventions have failed to improve mild to moderate depression or, in combination with high intensity psychological intervention, for moderate or severe depression.

The NICE guideline on depression in adults recommends that antidepressant treatment options should be discussed with the person taking into account side effects, discontinuation symptoms and potential interactions with concomitant medication or physical health problems. It also recommends that the choice of antidepressant should normally be a selective serotonin reuptake inhibitor (SSRI) in a generic form because SSRIs are equally effective as other antidepressants and have a favourable risk-benefit ratio. In addition, SSRIs are considerably safer in overdose than tricyclic antidepressants (TCAs) and are generally better tolerated than antidepressants from other classes. In adults with co-

morbidities, the NICE guideline on depression in adults with a chronic physical health problem recommends to consider using citalopram or sertraline because they have less propensity for interactions.

When prescribing antidepressants other than SSRIs, the increased likelihood of stopping treatment due to side effects must be considered. Certain antidepressants are associated with specific cautions, contraindications and monitoring requirements; for example, TCAs are associated with the greatest risk in overdose and can exacerbate cardiac arrhythmias.

The NICE Pathway on [depression](#) brings together all related NICE recommendations and supporting information on this topic in a set of interactive topic-based diagrams. The Clinical Knowledge Summaries information on [depression](#) gives a general overview of prescribing considerations.

## New evidence

A [systematic review](#) and [network meta-analysis](#) (Cipriani et al. 2018) compared the efficacy and acceptability of antidepressants for the acute management of major depressive disorder in adults. The primary outcomes were efficacy and acceptability of treatment. 'Efficacy' was defined as a reduction of 50% or more of the total score on a standardised observer-rating scale for depression and 'acceptability' as the proportion of participants who withdrew for any reason. Secondary outcomes included final depression score, remission rate and the proportion of participants dropping out because of side effects.

This systematic review included 522 double-blind [randomised controlled trials](#) (RCTs) that were carried out between 1976 and 2016, included 116,477 participants and compared 21 antidepressants as monotherapy with placebo (n=29,425) or another antidepressant (n=87,052). The median duration of acute treatment was 8 weeks. The mean age of the participants was 44 years, and 62.3% of the participants were women. In 89% of the included studies, most of the participants had moderate to severe major depressive disorder, with a mean baseline severity score of 25.7 on the [Hamilton Depression Rating Scale 17-item](#) (a score of 24 or more indicated severe depression). Most of the studies (83%) were multicentre with 48% of the studies including people from North America and 27% of the studies including people from Europe. Seventy-seven percent of the studies recruited outpatients only. Rescue medicines (such as benzodiazepines or other sedative hypnotics) were allowed in 36% of studies. Quasi-randomised trials and RCTs with 20% or more participants with bipolar disorder, psychotic depression or treatment-resistant depression, or with a serious medical comorbidity were excluded.

The primary analysis was based on 474 studies (n=106,966) that included prescribed antidepressants within in the licensed dose range. In 432 placebo-controlled RCTs (n=102,443), all antidepressants were more effective than placebo in reducing depressive symptoms over an 8-week period with [odds ratios](#) (OR) ranging between 2.13 (95% [credible interval](#) [CrI] 1.89 to 2.41) for amitriptyline and 1.37 (1.16 to 1.63) for reboxetine. For tolerability, agomelatine (OR 0.84, CrI 0.72 to 0.97) and fluoxetine (OR 0.88, CrI 0.80 to 0.96) were associated with fewer dropouts than placebo. Clomipramine was found to be worse than placebo (OR 1.30, CrI 1.01 to 1.68). In addition, all antidepressants were associated with higher withdrawal rates because of side effects (OR ranging between 1.64 and 4.44) compared with placebo.

In 194 head-to-head RCTs (n=34,196), agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine were more effective than other antidepressants (OR ranging between 1.19 and 1.96) whereas fluoxetine, fluvoxamine, reboxetine, and trazodone were the least effective (OR range between 0.51 and 0.84). In terms of acceptability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline and vortioxetine were better tolerated than other antidepressants (OR range between 0.43 and 0.77). Amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine,

trazodone and venlafaxine were associated with higher dropout rates (OR ranging between 1.30 and 2.32). The [GRADE framework](#) generally found the evidence to be moderate quality for agomelatine, citalopram, escitalopram and mirtazapine, and low to very low quality for amitriptyline, bupropion, clomipramine, nefazadone and vortioxetine.

Smaller differences in the efficacy and acceptability of antidepressants were found when placebo-controlled RCTs were included in the analysis, whereas there was more variability in efficacy and acceptability in the head-to-head RCTs. The authors state that this could be explained by factors such as the randomisation ratio and the expectation of receiving an active treatment, the therapeutic setting or the frequency of study visits. Dropouts were reported to occur more often in the placebo-controlled trials. In addition, antidepressants start to work after weeks of treatment, therefore participants who dropped out earlier tend to have poorer responses than those who remain on treatment, which are carried forward to the end of the trial by the last observation carried forward analysis (this approach can also effect the estimates of treatment effect). The authors suggest that depressive symptoms tend to spontaneously improve over time and this phenomenon contributes to the high percentage of placebo responders in antidepressant trials. The authors also reported a 'novelty effect' with new or experimental antidepressants showing a better efficacy profile compared with old antidepressants in the head-to-head comparisons. This may reflect the subjective perception that new treatments are more effective and better tolerated or highlight selective analysis and reporting bias when treatments were first launched.

## Commentary

### Commentary provided by NICE

This network meta-analysis was an update and extension of a previous study ([Cipriani et al. 2009](#)) that looked at 12 antidepressants in a head-to-head comparison only. This updated study (Cipriani et al. 2018) included a more comprehensive list of 21 antidepressants and placebo. The study reported few differences between antidepressants when all data were considered. There was more diversity in the range of efficacy and dropout patterns seen across the head-to-head comparisons than the meta-analysis of antidepressants compared with placebo. The authors state they focused on head-to-head studies and emphasised the certainty of the retrieved evidence to make the results as relevant and robust as possible to inform clinical practice.

There were a number of advantages of this study. Firstly, there was a large number of people included in the network meta-analysis suggesting that the results were more precise because of the high [statistical power](#) and the findings were supported by previous reviews on the same subject. Secondly, to increase the methodological rigour of the contributing evidence, the authors included only double-blind trials, which were generally very similar in design and conduct. Thirdly, the larger evidence base obtained through a comprehensive search for published and unpublished information, allowed them to find results for additional important outcomes, such as remission, change in mood symptoms and dropouts because of side effects, as well as highlight a number of methodological issues such as sponsorship, dosing schedule, study precision, and novelty effect.

A weakness of this study is that it summarises evidence of differences between antidepressants when prescribed as an initial treatment only and not for subsequent treatment. In addition, this study did not cover important clinical issues that might inform treatment decision making in routine clinical practice (for example, specific side effects, withdrawal symptoms, or combination with non-pharmacological treatments). Some of the side effects of antidepressants occur over a prolonged period, meaning that positive results need to be interpreted with caution, because the trials in this network meta-analysis were of short duration.

Further limitations highlighted by the authors included the variation in quality of many comparisons among antidepressants suggesting variation in the certainty of the results. Many trials did not report

adequate information about [randomisation](#) and [allocation concealment](#), which restricts the interpretation of these results. There was no formal cost-effectiveness analysis. The inclusion criteria for the studies were restrictive and excluded people with psychotic or treatment-resistant depression, which might limit the applicability of the results to these clinical subgroups. There was a possibility that some studies may be absent or the same study had been counted twice in the analyses.

Overall, the study found few differences between antidepressants when all data were considered, while there was more diversity in the range of efficacy and dropout patterns seen across the head-to-head comparisons than the meta-analysis of antidepressants compared with placebo. This study supports the NICE recommendations on using SSRIs as first choice as they have a favourable risk-benefit ratio. People with depression should be treated in line with the NICE guidelines on [depression in adults](#) (being [updated](#)) and [depression in adults with a chronic physical health problem](#), and the NICE quality standard on [depression in adults](#).

## Study sponsorship

This study was funded by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre and the Japan Society for the Promotion of Science.

## References

Cipriani A, Furukawa T, Salanti G et al. (2018). [Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis](#). The Lancet 391: 1357–1366

Cipriani A, Furukawa T, Salanti G et al. (2009). [Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis](#). The Lancet 373: 746–758.

### About this Medicines Evidence Commentary

Medicines Evidence Commentaries form part of [NICE's Medicines Awareness Service](#) and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

[Visit Evidence Search](#)

Copyright © NICE 2018. All rights reserved. Subject to [Notice of rights](#).