Review: clinically important differences between antidepressants

QUESTION

Question: What are the effects of the 12 most commonly prescribed new generation antidepressants for moderate to severe major depression in adults?

Outcomes: Response to treatment at 8 weeks, defined as the proportion of patients having a 50% or greater reduction from baseline in Hamilton Depression Rating Scale or Montgomery–Asberg depression rating scale or those scoring "much improved" or "very much improved" on the clinical global impression; discontinuation as a measure of acceptability of treatment defined as the number of patients who terminated the study early for any reason during the first 8 weeks of treatment.

METHODS

Design: Systematic review with meta-analysis (pairwise with random effects model and mixed treatment meta-analysis).

Data sources: Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials registers (searched November 2007).

Study selection and analysis: Randomised controlled trials comparing any of the following new generation antidepressants being used as monotherapy to treat adults with unipolar major depression: duloxetine, velanfaxine, sertraline, bupropion, citalopram, escitalopram, fluoxetine, minacipran, fluvoxamine, mirtazapine, paroxetine and reboxetine were included. Two independent reviewers evaluated the methodological quality of the trials and extracted the data. Responders to treatment were calculated on a conservative intention to treat basis (missing results assumed non-responders). Studies comparing the same interventions were combined using a random effects meta-analysis. Heterogeneity was investigated using the I^2 statistic. Secondly, a mixed treatment meta-analysis was undertaken using a Bayesian random effects Markov chain Monte Carlo model (in WinBUGS) to combine direct (treatments compared with each other in a randomised controlled trial) and indirect evidence (combining between trial treatment results when drugs are compared with a common comparator in separate studies) for any given pair of treatments. The probability that each drug was the most effective was assessed by calculating the odds ratio for each drug compared with an arbitrary common control; iterations of the Markov chain in which each drug had the highest odds ratio, second highest, etc, were counted and drugs ranked accordingly.

MAIN RESULTS

117 trials were eligible for inclusion in the mixed treatment meta-analysis. Most were carried out in North America and Europe. The mean duration of the studies was 8.1 weeks and only 14 studies had a follow-up longer than 12 weeks. There were on average 110 participants per group and 53 studies included people aged 65 years or younger. Mixed treatment analysis allowed 84 pairwise comparisons. Generally, mirtazapine, escitalopram, sertraline and venlafaxine were more effective than duloxetine, fluoxetine, paroxetine, reboxetine and fluvoxamine. Reboxetine was less effective than all other antidepressants tested. Escitalopram and sertraline were associated with fewer discontinuations than duloxetine, paroxetine, reboxetine, fluvoxamine and venlafaxine (see webextra table for the cumulative probabilities of each antidepressant being among the four best treatments in terms of efficacy and acceptability).

CONCLUSIONS

There are clinically important differences between antidepressants. Escitalopram and sertraline have the most favourable balance between benefits and acceptability and may be the best choice when starting treatment for moderate to severe major depression.

ABSTRACTED FROM

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COMMENTARY

This meta-analysis by Cipriani and colleagues is a significant piece of work that potentially influences clinical practice. Its publication in *The Lancet* is an acknowledgement of this, the independence of its authors and the novelty of its methodology. It is the first time that a multiple treatments meta-analysis technique has been applied to antidepressants. Its findings, in general, support a growing body of data suggesting differences in efficacy between antidepressants. Using more conventional meta-analytic techniques, venlafaxine and mirtazepine were found to be more likely to lead to remission than other antidepressants by the National Institute for Health and Clinical Excellence (NICE).[1] However, NICE refrained from making recommendations about using the drugs in preference to others due to concerns about effect sizes. It can be argued that randomised controlled trials (RCTs) are only designed to test statistical, rather than clinical, significance[2] and the British Association for Psychopharmacology (BAP) guidelines have accepted the superiority of a small number of antidepressants and recommended these in severe depression and situations where efficacy is of overriding importance.[3] This list of drugs includes venlafaxine and escitalopram, both supported by the present analysis. Perhaps the surprise in the analysis by Cipriani and colleagues is that sertraline was also shown to be superior to other newer antidepressants. It was less surprising that escitalopram and sertraline also proved to be the best tolerated (in terms of least likely to lead to dropouts in RCTs). Therefore, given the lower acquisition cost of sertraline, it seems a not unreasonable suggestion by the authors that this should be considered as a firstline treatment. The one caveat is the possibility that it may be easier to use sub-therapeutic doses of sertraline than other selective serotonin reuptake inhibitors, with the impact of dosage on the meta-analysis findings being unclear, and specifically whether the benefits are evident at just 50 mg/day. However, extrapolating from these findings in general, there is support for an extension of the BAP guidelines that for the more severely ill and/or those who have failed to respond to firstline treatments, one should consider the possibility of venlafaxine, mirtazepine, escitalopram and possibly sertraline.

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