EDITORIAL

How effective are antidepressants?

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ALL ANTIDEPRESSANTS ARE MORE EFFICACIOUS THAN PLACEBO IN ADULTS WITH MAJOR DEPRESSIVE disorder, a systematic review and network meta-analysis has found.[1]

Double-blind, randomised controlled trials were identified from the Cochrane Central Register of Controlled Trials and other large databases. Placebo-controlled and head-to-head trials of 21 antidepressants (a selection of first-generation and all approved second-generation antidepressants) were included.

Overall, 522 trials (436 published and 86 unpublished) with a total of 1,164,77 participants were analysed. Most participants had moderate to severe depression and the median trial period was eight weeks. The primary outcomes were efficacy and acceptability, defined respectively as the response rate (a reduction ≥50% in the rating score) and all cause discontinuation rate.

All antidepressants were significantly more efficacious than placebo, with odds ratios (OR) ranging from 2.13 for amitriptyline (95% CI: 1.89-2.41) to 1.37 for reboxetine (95% CI: 1.16-1.63). Agomelatine and fluoxetine were significantly more acceptable than placebo OR 0.84 (95% CI: 0.72-0.97) and 0.88 (95% CI: 0.80-0.96) respectively whereas clomipramine was significantly less acceptable than placebo OR 1.30 (95% CI: 1.01-1.68).

'Efficacy and tolerability are not the only criteria which should be considered'

Compared with the placebo-controlled trials, the head-to-head trials found greater differences between drugs. When all trials were considered, the ranges of significant ORs for one antidepressant compared with another were 1.15-1.55 for efficacy and 0.64-0.83 for acceptability. When the analysis was restricted to head-to-head trials the ranges were expanded to 1.19-1.96 and 0.43-0.77 respectively.

When all data were considered, escitalopram, mirtazapine, paroxetine, agomelatine and sertraline were found to have a relatively higher response and lower dropout rate than other antidepressants. Head-to-head studies suggested that agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine and vortioxetine were the most efficacious; agomelatine, citalopram, escitalopram, fluoxetine, sertraline and vortioxetine were the best tolerated.

The authors of a *BMJ* editorial have used the mean OR (1.66) from this meta-analysis to calculate an antidepressant response rate of about 50% compared with 40% on placebo, NNT 8-10.[2] This would suggest that antidepressants have more modest benefits than previously thought (response rate 50% compared with 30% on placebo, NNT 5)[3] but is comparable to a meta-analysis submitted to the FDA which found that 82% of the response to antidepressants was a placebo effect.[4]

Six of the 21 included antidepressants are not licensed for use in the UK whereas two of the 11 most commonly prescribed antidepressants in the UK, dosulepin and lofepramine,[5] were not included in the meta-analysis. NICE recommends that dosulepin should no longer be prescribed and there can be no argument with its exclusion.[5] However, compared with other tricyclics lofepramine has fewer side effects, is less toxic in overdose[6] and may be a good alternative to SSRIs in elderly patients, although it is expensive.[7]

Of those antidepressants found to have relatively high efficacy and acceptability, NICE does not recommend the use of agomelatine and recommends vortioxetine as third line only.[8]

Efficacy and tolerability are not the only criteria which should be considered when choosing an antidepressant. Tricyclics, with the exception of lofepramine, are the most toxic in overdose and mirtazapine and venlafaxine have intermediate toxicity. Citalopram is more toxic than other SSRIs.[9] Propensity to cause discontinuation syndrome should also be considered: antidepressants with a relatively short half life such as paroxetine are most likely to cause this.[6]

This study provides the most comprehensive evidence to date that antidepressants do work, at least in the short term, although most of the benefit is due to the placebo response. With regard to antidepressant choice, the findings are less clear cut than those from an earlier study[10] which recommended sertraline as a 'best buy'. However, taking into account efficacy, side effects, toxicity, risk of discontinuation syndrome and cost, I see no reason to change the endorsement of sertraline.

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