Efficacy of antidepressants in adults

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Education and debate

Efficacy of antidepressants in adults

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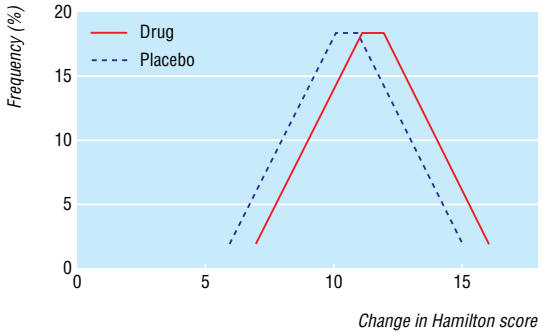
Most people with depression are initially treated with antidepressants. But how well do the data support their use, and should we reconsider our strategy?

The National Institute for Health and Clinical Excellence (NICE) recently recommended that antidepressants, in particular selective serotonin reuptake inhibitors, should be first line treatment for moderate or severe depression.[1] This conclusion has broadly been accepted as valid.[2] The message is essentially the same as that of the Defeat Depression Campaign in the early 1990s, which probably contributed to the 253% rise in antidepressant prescribing in 10 years.[1] From our involvement in commenting on the evidence base for the guideline we believe these recommendations ignore NICE data. The continuing concern that selective serotonin reuptake inhibitors may increase the risk of suicidal behaviour[w1 w2] means there needs to be further consideration of evidence for the efficacy of antidepressants in adults as there has been in children.



Normal distribution of scores for Hamilton rating scale for depression with mean score of 11.5 for antidepressant and 10.5 for placebo

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Efficacy

Although the NICE meta-analysis of placebo controlled trials of selective serotonin reuptake inhibitors found significant differences in levels of symptoms, these were so small that the effects were deemed unlikely to be clinically important.[1] The conclusion that the drugs had clinically important benefits was based on analysis of response and remission rates. However, in our comments on the draft guidelines, we pointed out that these categorical outcomes were derived from the same continuous data for symptoms scores that were found to show no clinically relevant effects. As NICE notes, "dichotomising scores into remission and non-remission creates an artificial boundary, with patients just over the cut-off score often being clinically indistinguishable from those just under the cut-off."[1]

The hypothetical data in the figure show how small differences may be magnified by transformation of continuous data into categorical data.[3] In this example, response was defined as a minimum 12 point improvement on the Hamilton rating scale for depression. Difference in mean change of scores between drug and placebo groups was 1 point. This scenario yields response rates of 50% in the drug condition and 32% in the placebo condition. Thus, if improvement is normally distributed and the criterion for response is close to the mean improvement rate (which it generally is), a very small difference in symptom score can push a large proportion of patients into different categories.

The small effects found on continuous measures are consistent with results of other recent meta-analyses of symptom scores. Khan et al found a 10% difference in levels of symptoms in two meta-analyses,[4 5] and Kirsch et al included unpublished studies in their latest analysis and found an overall mean difference of 1.7 points on the Hamilton scale.[6] No research evidence or consensus is available about what constitutes a clinically meaningful difference in Hamilton scores, but it seems unlikely that a difference of less than 2 points could be considered meaningful. NICE required a difference of at least 3 points as the criterion for clinical importance but gave no justification for this figure.[1] The most commonly used 17 item version of the Hamilton scale has a maximum score of 52 and contains seven items concerning sleep and anxiety, with each item on sleep scoring up to 6 points. Hence any drug with some sedative properties, including many antidepressants, could produce a difference of 2 points or more without exerting any specific antidepressant effect. Other recent meta-analyses that present categorical outcomes also find modest differences of between 14% and 18% in improvement or response rates.[w3-w5]

References w1-w20 are on bmj.com

Severity of depression

A key claim in the NICE guideline is that the superiority of antidepressants over placebo correlates positively with the severity of depression being treated. This belief is an old one. In 1958 Kuhn suggested that endogenous depression was more responsive to antidepressants than neurotic or reactive depression, which was generally regarded as less severe.[7] Regression to the mean may account for this impression since it entails that people with more severe depression at baseline will show greatest overall levels of improvement. But it does not explain drug-placebo differences, because greater improvement among patients with more severe depression occurs regardless of whether they are treated with a drug or placebo.

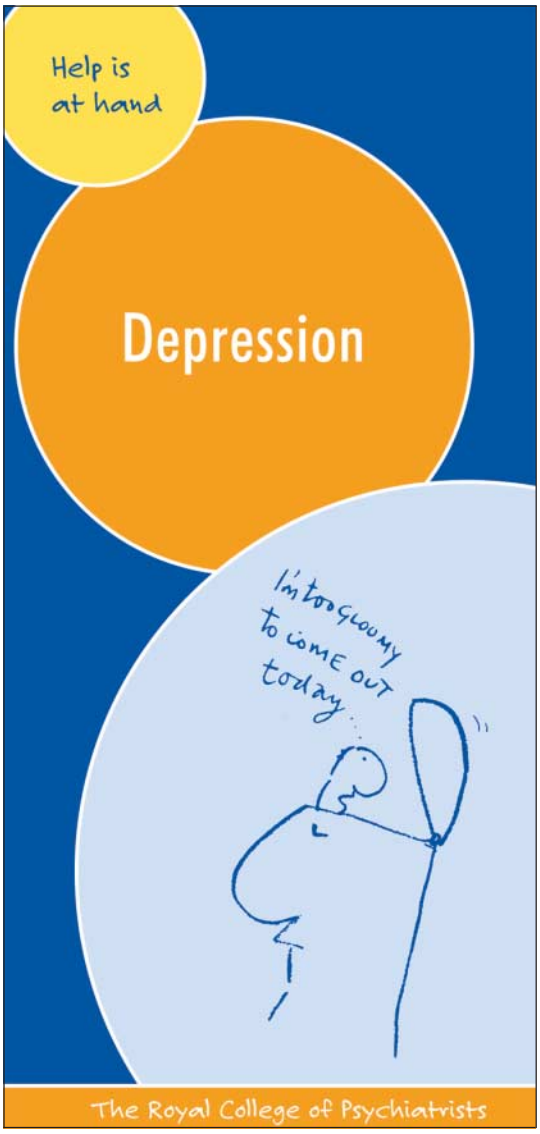
An early review of controlled trials found that evidence about whether endogenous symptoms predicted response was inconsistent.[8] Recent evidence comes from post-hoc analysis in trials with otherwise negative results[w6 w7] and from meta-analyses. The meta-analysis by Angst et al is often cited in support of the severity hypothesis, but severity effects were weak and mostly non-significant.[9] Effects in another meta-analysis were more impressive, but data were provided only for investigational antidepressants and not established ones, where the evidence seemed to be weaker.[10] In contrast, another recent meta-analysis found no relation between severity and antidepressant effect,[11] and a meta-analysis of older studies showed that differences between antidepressants and placebo were smaller and non-significant in inpatient trials compared with outpatient trials.[12] The NICE meta-analysis failed to find a consistent gradient of effect from "moderate" (Hamilton score 14-18) through "severe" (19-22) to "very severe" depression (≥ 23).[1] In fact, the middle group, which would generally be referred to as moderately depressed, tended to show larger effects than either of the other two, but numbers of studies were small.

Thus there seems to be little support for the suggestion that recent failure to find marked differences between antidepressants and placebo is due to recruitment of patients with mild depression that is less responsive to antidepressants.[1] Indeed, in the meta-analysis by Kirsch et al, all but one of the trials were conducted in patients with severe to very severe depression according to NICE criteria.[6] The possibility that patients in the mid-range of severity show a greater antidepressant response, as suggested by the NICE data and by Joyce and Paykel,[8] would not be expected from a simple biological effect. It may indicate that this group is more susceptible to some methodological artefact such as infringement of the double blind (see below).

Methodological issues in antidepressant trials

Several commentators have suggested that the small effects of antidepressants compared with placebos may be attributable to methodological factors or selective presentation of data from antidepressant trials.[w8-w10] These include concerns that trials of antidepressants may not be truly double blind. This is because participants may be able to detect differences between placebos and drugs because the drugs cause noticeable physiological effects including, but not limited to, recognised side effects. Other concerns include the validity of outcome measures, that discontinuation effects may confound continuation trials, and that results may be inflated by exclusion of people who withdraw early from the analysis. Evidence also shows that trials of antidepressants with negative results are less likely to be published than those with positive results and that, within published trials, negative outcomes may not be presented.[13]

A neglected aspect of antidepressant trials is the substantial heterogeneity of their findings.[12] Although many trials do find antidepressants are superior to placebo, many do not, including some of the largest and most well known landmark trials such as the Medical Research Council trial and the early National Institute for Mental Health trial.[w11 w12] In addition, many trials find that substances as diverse as methylphenidate, benzodiazepines, and antipsychotics



Campaigns raising awareness of depression have contributed to increased prescribing of antidepressants

Summary points

- Recent meta-analyses show selective serotonin reuptake inhibitors have no clinically meaningful advantage over placebo
- Claims that antidepressants are more effective in more severe conditions have little evidence to support them
- Methodological artefacts may account for the small degree of superiority shown over placebo
- Antidepressants have not been convincingly shown to affect the long term outcome of depression or suicide rates
- Given doubt about their benefits and concern about their risks, current recommendations for prescribing antidepressants should be reconsidered

can have antidepressant effects, suggesting that these effects may be attributable to non-specific pharmacological or psychological mechanisms.[w10]

Effect of antidepressants

Longitudinal follow-up studies show very poor outcomes for people treated for depression both in hospital[14] and in the community,[15] and the overall prevalence of depression is rising despite increased use of antidepressants.[16] Two studies that prospectively assessed outcome in depressed patients treated naturalistically by general practitioners and psychiatrists found that people prescribed antidepressants had a slightly worse outcome than those not prescribed them, even after baseline severity had been taken into account.[17 18] No comparable studies could be found that showed a better outcome in people prescribed antidepressants.

Some authors have suggested a causal association between increased antidepressant prescribing since 1990 and reduction of overall suicide rates observed in some countries.[w13 w14] However, others have pointed out that falls in overall suicide rates started long before this period,[w15-w17] and suicide rates have increased in some age groups[w15] and some countries[w18] despite increased antidepressant prescribing. Meta-analyses of data from controlled trials have not found reduced rates of suicide or suicidal behaviour in drug arms compared with placebo arms.[4 5 w19 w20]

Conclusions

The NICE review data suggest that selective serotonin reuptake inhibitors do not have a clinically meaningful advantage over placebo, which is consistent with other recent meta-analyses. In addition, methodological artefacts may account for the small effect seen. Evidence that antidepressants are more effective in more severe conditions is not strong, and data on long term outcome of depression and suicide do not provide convincing evidence of benefit. In children, the balance of benefits to risks is now recognised as unfavourable. We suggest this may also be the case for adults, given the continuing uncertainty about the possible risk of increased suicidality as well as other known adverse effects. This conclusion implies the need for a thorough re-evaluation of current approaches to depression and further development of alternatives to drug treatment. Since antidepressants have become society's main response to distress, expectations raised by decades of their use will also need to be addressed.

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Contributors and sources: Both authors have conducted separate meta-analyses of antidepressant trials and reviews of antidepressant literature. JM has recently obtained an MD in antidepressant research methodology. The article draws on these sources, as well as the data contained in the NICE review. JM and IK contributed to the response to the NICE review. JM had the idea to write the paper. JM and IK drafted and revised the current manuscript. JM will act as guarantor.

Competing interests: IK has received consulting fees from Squibb and Pfizer. JM is co-chair of the Critical Psychiatry Network.

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