Are antidepressants clinically useful? Conclusion of a decade of debate

During the last decade, a number of meta-analyses have questioned the clinical usefulness of antidepressants, and exposed a significant publication bias and low effect size in comparison to placebo (1-9). The most important implication has been that antidepressants might not have any effect at all in mildly depressed patients (1,4,5). Several authors and agencies, such as the National Institute for Health and Clinical Excellence (NICE), have suggested the utilization of "alternative" treatment options (e.g., exercise and psychotherapy) in mildly depressed patients, and pharmacotherapy only for the most severe cases. An immediate consequence of this is that patients suffering from mild depression may be deprived from receiving antidepressants.

The Kirsch hypothesis concerning depression (10,11) is that there is a response which lies on a continuum from no intervention at all (e.g., waiting lists) to neutral placebo, then to active and augmented placebo including psychotherapy, and finally to antidepressants, which exert a slightly higher efficacy probably because blinding is imperfect due to side effects (enhanced placebo). This hypothesis has triggered much interest from the mass media and from intellectuals outside the mental health area, often with a biased and ideologically loaded approach (12).

Several authors have criticized the above hypothesis by focusing on the limitations of randomized controlled trials, on some limitations of Hamilton Depression Rating Scale (HDRS), and on the fact that the effectiveness of antidepressants in clinical practice is usually optimized by sequential and combined therapy approaches (13,14).

Two early efforts to re-analyze the Kirsch data set using different methodological approaches (15,16) independently reported results quite similar between them but different from those published by Kirsch. A recent multi-meta-analysis (17) utilized the Kirsch et al dataset and concluded that the most probable effect size of antidepressants relative to placebo is 0.34 (0.27-0.42) and that there is no significant effect of the initial severity of depression. The most probable raw HDRS score change after treatment with antidepressants is 2.82 (2.21-3.44). The same analysis showed that antidepressants are not equally effective, with venlafaxine being more effective than the rest and fluoxetine being the least effective.

The argument that a standardized mean difference (SMD) of 0.30-0.35 versus placebo is a weak one, suggesting that the treatment is not really working or does not make any clinically relevant difference, neglects the fact that such an effect size is the rule rather than the exception for efficacious treatments in psychiatry and medicine (e.g., 18). For comparison, one should look at the meta-analyses of the efficacy of medications for acute mania, reporting an SMD of 0.22-0.48

(19,20) while mania is clinically one of the easiest-to-treat acute psychiatric conditions.

The series of meta-analyses performed during the last decade made antidepressants perhaps the best meta-analytically studied class of drugs in the whole of medicine. The results of the recent multi-meta-analysis is likely to close the debate, suggesting that antidepressants are clearly superior to placebo and that their efficacy is unrelated to the initial severity of depression. Thus, there seems to be no scientific ground not to use antidepressants in mildly depressed patients.

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