Do antidepressants help much in comparison to placebo?

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The message that assignment to placebo does not increase the risk of suicidal behaviour in patients who participate in double-blind randomized trials (Khan et al., 2001) is important but hardly surprising. The risk of suicidal behaviour is one of the exclusion criteria in placebo-controlled trials. Patients with this risk should be omitted from study samples. The analysis of Khan et al. (2001) shows that the risk is not manifest in patients on placebo any more than in patients on antidepressants during trials.

What is surprising is the small difference (12.4%) between antidepressants and placebo in the decrease of the total Hamilton Depression Scale (HAMD) score. The authors give relevant reasons to explain the small difference. I would like to add another reason, which could explain the small difference even more. Total HAMD score is an arithmetical sum of scores of items that are not equal with respect to their relevance for the clinical severity of the disorder. I would expect that the active drug–placebo difference would be greater in scores of the item ‘depressed mood’ than in the items related to insomnia.

The importance of this approach was previously shown by Cole and Davis (1968). They summarized the results of collaborative studies organized by the Psychopharmacology Service Center of the NIMH and several other studies. Analysing the effect of phenothiazine neuroleptics compared to placebo they found that the active drugs were unequivocally more effective. Then, they divided the symptoms according to Bleuler (1911) into accessory (hallucinations, paranoid ideation and hostility) and fundamental symptoms (blunted affect, withdrawal–retardation, autistic behaviour and thought disorder). They found moderate change under placebo on accessory symptoms with little or no change during placebo administration in fundamental symptoms. The greatest amount of total clinical change occurred in the accessory symptoms when drug-induced change was added to change which occurred during placebo administration alone. However, the differential effect of phenothiazines as opposed to placebo was more striking on the fundamental symptoms of schizophrenia.

We should be cautious when evaluating the effects of second-generation antipsychotic drugs on negative symptoms, which are comparable to Bleulerian fundamental symptoms, as qualitatively different from the effects of the classical neuroleptics. This does not decrease their value in other effects where they differ from classical neuroleptics, e.g. effects on cognitive functions and absence of adverse extrapyramidal effects.

The small drug–placebo difference in the data reported by Khan et al. (2001) might be due to the use of only one global measure of efficacy without consideration of the drug–placebo difference in the effects on symptoms, or clusters of symptoms, as performed by Cole and Davis (1968). Unfortunately, data about the effects on symptoms – with rare exceptions (e.g. Kasper et al., 1995) – have not been published during recent years (Vinar, 1999).

References


O. Vinar, M.D., D.Sc.
Joint Laboratory Academic Science and State Institute Drug Control, Srobarova 48, 10041 Prague 8, Czech Republic.