

## Placebo response in depression: bane of research, boon to therapy

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Placebo controlled trials are appropriate when there is no existing treatment for a disorder, otherwise comparison trials are indicated. No new treatments should be introduced into medicine unless they have been shown, in randomised controlled trials, to be superior to existing treatments – or equivalent to existing treatments but cheaper or safer (Cochrane, 1989). In depression, new drugs are advertised as being superior to placebo even though, to gain regulatory approval, most are also tested against existing treatments. Doctors are not routinely provided with this information on comparative efficacy, effectiveness, safety and cost. The propriety of doing placebo controlled trials in depression was the topic of a recent article (Khan *et al*, 2000) and one of the conclusions was that the size of response in the placebo group was sufficient to justify continuing with placebo controlled trials, even though the existence of proven treatments would normally render placebo trials unethical. Sometimes antidepressant drugs, and for that matter cognitive-behavioural therapies, fail to show superiority over placebo, simply because the treatments are not very powerful compared with the change in the placebo control group. Two factors contribute to this change in the placebo group: the placebo effect proper, which arises from the sensitivity of patients to the encouragement that comes from being treated, plus improvement due to the natural history of remission and fluctuating symptom levels in the disorder.

### Could the placebo be the cure?

Kirsch & Sapirstein (1998) identified 19 placebo controlled trials of antidepressants that reported data on the progress of the placebo group. The placebo groups averaged a 1.5 standard deviation (s.d.) units of improvement, 75% of the overall progress shown by the drug groups, whose superiority over placebo groups was only 0.5 s.d.

Others (Quality Assurance Project, 1983; Joffe *et al*, 1996) had noted that the size of the progress attributed to the placebo group in depression trials was greater than the additional progress attributed to the drugs, so the finding is not new. What was new was that the correlation of 0.9 between the placebo effect and drug effect indicated that virtually all the variation between the improvement in the drug-treated groups in the different trials could be predicted by the response in the subjects randomised to the placebo groups. Discussants to the Kirsch & Sapirstein paper argued that it was a sampling phenomenon, and that the overall change depended on the sensitivity to non-specific factors of the whole pool of subjects, whether they were randomised to the placebo or drug group. Kirsch & Sapirstein used data from additional studies to separate the change in the placebo groups into change due to the placebo effect and change due to natural history. Their final conclusion was that one-quarter of the improvement observed in the drug-treated group was due to the active medication, one-quarter to natural history and half to the placebo effect. They then raised the possibility that the improvement attributed to the drug could even be a non-specific response to the side-effects generated by the medication. Moncrieff *et al* (1998), in a small meta-analysis of nine studies, addressed this and found that the superiority of drug over the active placebo atropine was reduced from an effect size of 0.50 in non-active placebo trials to an effect size of 0.21 with active placebos, consistent with the Kirsch & Sapirstein suggestion that people in trials respond more positively if they experience side-effects.

The article by Kirsch & Sapirstein in 1998 was published in an electronic journal that encouraged instant commentary. There was much, mainly centred on the question of whether antidepressants work at all, and on the probity of drawing conclusions from a meta-analysis of only 19 studies that had

data on the progress of the placebo groups, when the total literature is of the order of 1500 randomised controlled trials. Quitkin *et al* (2000) systematically reviewed the methodological issues raised by Kirsch & Sapirstein and concluded that, despite the large response in the placebo group, antidepressants are treatments that produce specific additional benefit. In an article in *Science*, Enserink (1999) commented on the difficulty facing drug trials when the response in the placebo group is disproportionately large compared with that of the drug-treated group. Discussion in the general media has continued, and is largely critical of antidepressants. The public have views about the benefits of antidepressants that are quite negative (Jorm *et al*, 2000) and such negative press can only further restrict the low rates of depression treatment. Poor coverage is an important public health problem (Andrews *et al*, 2000), given that depression ranks fourth in the world in terms of the global burden of disease (Murray & Lopez, 1996). It is important that health professionals and the public have correct information about the small but finite benefit that antidepressants can offer.

### Why is the change in the control group so large?

The original question remains: is it true that the change in the placebo group is abnormally large in depression? Comparing small meta-analyses can be misleading, because search and analysis strategies that differ from study to study can influence effect size calculations. The Quality Assurance Project conducted a series of meta-analyses across the major mental disorders in the mid-1980s (Quality Assurance Project, 1982, 1983, 1984, 1985a,b). The methodology of effect size estimation was the same for all studies and the results can be compared. In depression the placebo groups improved by 0.93 s.d. units, the active treatment groups by 1.54 s.d. units, with the placebo groups making 60% of the progress recorded in the drug groups. In no other disorder was improvement while on placebo this large, either in absolute terms or as a proportion of the change in the treatment group. In generalised anxiety disorder the DSM-III (American Psychiatric Association, 1980) figures were 0.71 s.d. units, 1.32 s.d. units and 53% (but now, the 6-month duration criteria in ICD-10 (World Health Organization, 1992) and DSM-IV (American

Psychiatric Association, 1994) would reduce the spontaneous remission component of the placebo response), in agoraphobia 0.35 s.d., 1.5 s.d. units and 23%, in obsessive-compulsive disorder they were 0.23 s.d., 1.08 s.d. units and 21%, while in schizophrenia the placebo groups made no progress and 0.89 s.d. units progress occurred in the treated groups. In depression, therefore, the extent of the response in the placebo-treated group is unusually large.

Change in any placebo group occurs for three main reasons: the encouraging effect of being in treatment, the effect of spontaneous remission while in treatment, and because people with chronic symptoms normally seek help when their symptoms are worst and, through natural fluctuations in severity, are likely to be improved when next assessed. While the last is true of all chronic disorders, the first two may be particularly germane in depression. Depression results in a lowering of mood and loss of vitality so that activity lessens and pleasurable activities are foregone. This self-defeating nature of depression is sensitive to the encouragement that comes from being in treatment. Good clinical care (Andrews, 1993) consists of a review of what the patient did and did not do, with encouragement to resolve problems and resume positive activity. Structured problem-solving and activity scheduling are systematic approaches to achieve these goals (Mynors-Wallis *et al*, 1995; Andrews & Jenkins, 1999) that have been demonstrated in randomised controlled trials to be effective. They are easily taught to general practitioners who like using these techniques, but it is somewhat harder to convince psychiatrists to do such simple things.

Spontaneous remission accounts for a considerable amount of the improvement observed. There are two naturalistic studies in which people have been interviewed on two occasions and the duration of intervening depressive episodes noted. McLeod *et al* (1992) reported from a sample of married persons that the median duration of DSM-III-R (American Psychiatric Association, 1987) episodes of depression was 10 weeks, with 75% having episodes of under 22 weeks. Kendler *et al* (1997) studied a population sample of women and found a median time to recovery of 6 weeks, with 75% recovering in 12 weeks. If the population time to recovery were a median of 8 weeks and 75% recovered within 16 weeks, then people recruited into

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a trial after being depressed for 8 weeks would have a 50% chance of remitting during the conduct of the usual 8-week trial. These two factors, response to encouragement and a 50% probability of spontaneous remission during the trial, could account for the considerable progress of placebo control groups in depression trials.

### Implications for research and therapy

The large size of the response in the placebo group reduces the power of trials and is an unwanted confound. Thase (1999) argues that as one-third of published trials of antidepressants fail to demonstrate efficacy, new strategies are needed in which sources of variance are systematically reduced. To increase the power of the trial he argues for the recruitment of subjects with moderate and severe illnesses and for a 4-week lead-in phase during which subjects receive psychoeducation about handling depression. Both steps are aimed at reducing the number still likely to respond to placebo once the trial proper has begun. Some of the difficulty of demonstrating the value of education programmes for primary care physicians might stem from the heterogeneity of the target population and the acceptance of recent onset cases who are likely to remit. These difficulties would lessen if we switched from placebo trials to comparison trials now that we have data on the small, but definite advantage, of the established antidepressant treatments (see Kraemer, 2000).

The size of the response to placebo might well be a bane to researchers and to the drug industry but, properly handled, it is surely a boon to busy clinicians and their patients. In the trials listed by Kirsch & Sapirstein (1998) no special efforts were made to potentiate the placebo effect, it was simply part of the control condition, and yet they calculated that it still accounted for half the observed improvement in the drug-treated group. Perhaps we should actively strive to potentiate the placebo effect when treating people with depression. The prescription of drugs alone

is not enough to get people fully better, whereas drugs, good clinical care, and elements of cognitive-behavioural therapy like structured problem-solving and pleasant event scheduling, may well be. Clinical practice guidelines frequently recommend that mild depression might be best treated without drugs. The application of these non-drug techniques to routine clinical practice is well described in standard texts (Andrews & Jenkins, 1999) and should be part of the armamentarium of all clinicians. Thus while Kirsch & Sapirstein's paper may have aroused concern among researchers and the lay public, it may have generated benefit if we can persuade clinicians and sufferers that potentiating the placebo effect with simple psychological strategies is good medicine.

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