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Innovation and placebos in research: a new design of clinical trial

Few therapies are more controversial today than placebos. Their clinical and research use have been extensively debated by researchers, regulators, and ethicists.[1–7] In a recent review, Maurizio Fava and colleagues[8] suggest that placebo responses are too high in psychiatry trials, which creates a ceiling effect for active drugs. The inability to show a clinical benefit beyond placebo for new drugs, they argue, increases the cost of drug development and inhibits development of new therapies.

Response rates with placebo in studies of antidepressants are substantial and have increased over time,[9] but is this really a problem in evaluating active therapies? Presumably, only if the measured effect difference for placebo versus drug is spurious or not generalisable. Although differences between placebo and active drug might be influenced by the selection of patients who enter trials, by the measurements that are used, or by the short duration of most trials, these factors are not problems just with use of placebos. By contrast, comparison trials that include placebo have arguably been the best defence against the waste of valuable time, health, and resources on useless or potentially toxic drugs. Although most areas of therapeutics have standard therapies, the evidence to support some current uses, especially off-label, is below the optimum. Add to this the suppression of negative results, which leads to an overestimate of benefit of standard treatments, and one might argue that every new therapy should be evaluated in a well-powered placebo-controlled trial.

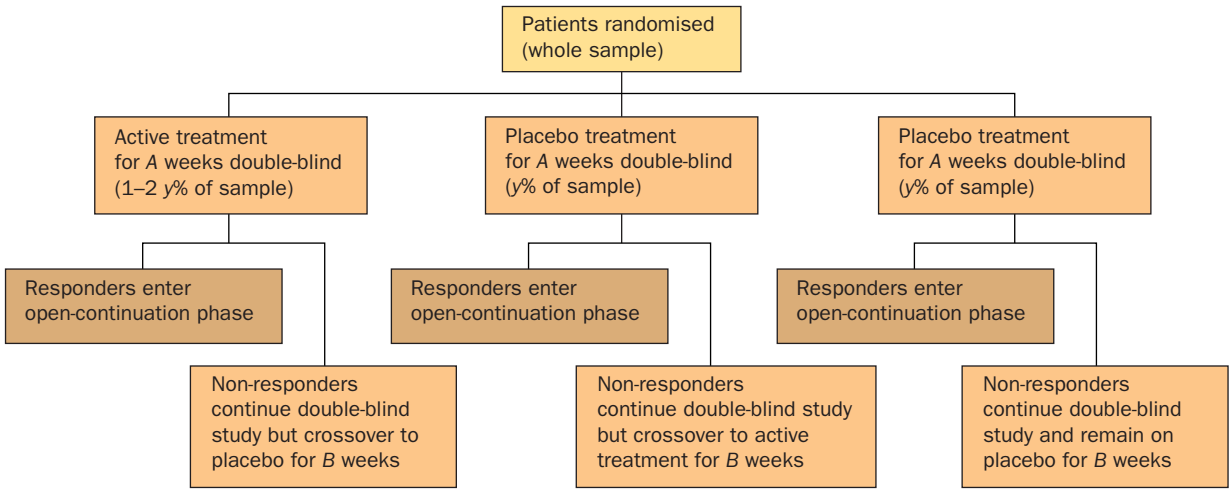
If placebo-controlled trials are necessary but inefficient as they are at present, what can be done? Fava and colleagues[8] argue for a new trial design aimed at decreasing the placebo response rate. Their name for the design—sequential parallel comparison—is somewhat confusing, because it is a partial crossover design. This is a two-phase design in which phase 1 is randomisation to three groups, two of which receive placebo and one receives active treatment (figure). At the end of phase 1, responders in the active treatment group move to an open-label continuation in phase 2, while non-responders continue in a double-blind mode but are switched to placebo. The responders to placebo at the end of phase 1 also enter an open-label continuation phase 2, while non-responders continue in a double-blind phase 2 and cross over to active drug or remain on placebo. In Fava's antidepressant study example, each phase is short (6 weeks) and outcomes from each blinded phase are pooled for analysis.

This unusual cross-over design[8] has several atypical features: (i) the number of patients in each of the three groups is unbalanced to yield maximum power and is based on expected response rates for placebo and intervention; (ii) responders' outcomes are based on the first 6 weeks while non-responders may have the same outcomes counted in both 6 week phases; (iii) placebo non-responders have a 50/50 chance of continuing on in a placebo group even after it is known that they have not responded; and (iv) those who do not respond to active treatment are switched to placebo but the placebo-phase data are not counted. None of the data from the open-treatment arms is used in the analysis.

Although there is little doubt that cross-over designs reduce sample size because the patients serve as their own controls, thus generally reducing variation, there are several aspects of Fava's design[8] that would be difficult in many research environments. First, the deliberate selection of placebo non-responders introduces bias and impedes generalisability of the trial. We feel that placebo responses should be explored and used therapeutically, not suppressed. Second, the prolonged exposure to placebo in non-responders would be unlikely to pass research ethics review and, if passed, would require a consent process that made it obvious to participants that they were much more likely to receive placebo in the first phase. This unequal allocation would itself probably alter recruitment and the placebo response rate of those recruited. Third, not all of the generated data are included in the final analysis. Fourth, there is no assignment to active drug followed by active drug; thus any delayed response will be missed. Fifth, although Fava and colleagues adjust for the dual-phase data being available for some of the patients (double counting), this calculation as well as the weighting system and the summary formulae are inscrutable to all but experienced statisticians. This inscrutability is a recurring problem for those who are mathematically-challenged clinicians but wish to understand, critique, use, or improve research data.

Fava and colleagues[8] should be congratulated on their pursuit of effective study designs that provide efficacy

Fava and colleagues' study design[8]



A and *B*=duration of first and second periods, respectively. *y* determines sample size of each group and is based on maximum power calculation.

answers quickly. As they suggest, their proposed design will need to be empirically evaluated. In the meantime, designs that address the more pressing issue of appropriate evaluation of investigative therapies while not unduly exposing patients to only placebo are urgently needed. A simple add-on trial comparing new therapy plus standard therapy versus standard therapy alone might suffice if it is known that the new therapy does not interact with the standard therapy and if the efficacy of the standard therapy in the population being studied is well characterised. But, usually, neither of these features is satisfied. A 2×2 factorial design involving standard and new therapies has four groups: double placebo, new therapy, standard therapy, and a combination of standard plus new therapies. With a 1:1:1:1 allocation ratio, there are two estimates of the efficacy of the new therapy: the difference between the new therapy group mean and the double-placebo group mean, and the difference between the combination standard-therapy/new-therapy group mean and the standard-therapy group mean. These two estimates are pooled to measure the overall efficacy of the new therapy by computing the mean of the two estimates. These two estimates should be similar to each other, provided the new therapy does not interact with the standard therapy. However, half of the patients are given either the double placebo or the new therapy of yet unproven efficacy. This design might present an ethical problem if the standard therapy has excellent efficacy and clinicians are reluctant to deny patients access to it. More sophisticated fractional factorial allocation is possible if there is more than one standard therapy.[10] This design can be applied without a placebo-only group but is more complicated to manage.

The bottom line is that clinicians should be aware of the power of the placebo effect, the importance of placebo in the evaluation of new therapies or new combinations of therapies, and the ethical controversies raging over the appropriate use of placebos in research and clinical care.[1] For the moment, alternative placebo-controlled trial designs will remain mainly the interest of researchers and research ethics boards only.

We have no conflict of interest to declare.

*Anne Holbrook, Charles Goldsmith

Centre for Evaluation of Medicines, St Joseph's Healthcare, Hamilton, Ontario, Canada L8N 1G6 (AH, CG);
Division of Clinical Pharmacology (AH), Department of Medicine (AH), and Department of Clinical Epidemiology and Biostatistics (AH, CG), McMaster University, Hamilton, Ontario, Canada
(e-mail: holbrook@mcmaster.ca)

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A riddle wrapped in a mystery inside an enigma: Brainerd diarrhoea turns 20

In December, 1983, a resident of Brainerd, Minnesota, had sudden onset of an explosive watery diarrhoeal illness that would last many months, afflict over 120 of his neighbours, and come to bear the name of this rural community.[1] In the ensuing 20 years, eight additional outbreaks have been reported as Brainerd diarrhoea, each characterised by watery diarrhoeal illness of impressively long duration with acute onset and the same striking constellation of symptoms, including