How many good antidepressant medications have we missed?

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The current methodology used to assess the clinical efficacy of antidepressant candidate drugs has been plagued in recent years by the failure of over 50% of controlled trials to separate placebo from established antidepressants and experimental medications.[1] In contrast, a "negative" trial is one in which the active comparator, but not the antidepressant candidate, is significantly better than placebo. Consecutive failed studies have led several pharmaceutical firms to abandon the clinical development of agents with great antidepressant potential. Some of the factors possibly accounting for such a poor track record are addressed here.

Once antidepressant medications have been demonstrated to be safe for human use, they generally have to prove superior to placebo in at least 2 randomized, double-blind, placebo-controlled studies to be approved by regulatory agencies. It is always striking to see the magnitude of the placebo response in such trials. This is a confounding factor that diminishes the difference between the active agents and placebo. One has to realize, however, that patients included in such studies receive care and monitoring that are far superior to those obtained in most clinical settings. Indeed, they meet a study coordinator, or a nurse, and a psychiatrist at screening and weekly thereafter. They also have 24-hour access to study personnel through a pager system in case of complications, significant discomfort and/or cumbersome side effects. This certainly beats having to wait in line at the primary care centre to see the treating physician or waiting for phone calls to be returned by the prescriber! The placebo response in short-term trials is, however, short lasting. If such placebo responders are entered into a placebo prolongation, they generally relapse quite rapidly, whereas if they are assigned to a medication arm, they will often remain well.[2] The significant placebo response is not a new problem, but it has been increasing in the last decade. Some factors that may contribute to this trend are discussed below.

Clinical trials have become a lucrative business, and nowadays the so-called pivotal studies designed to lead to drug approval are largely carried out in private centres. Although many of these organizations perform well, others are not consistently operated by experienced personnel. Even academic centres may not shelter the industry from failed studies, because critical stages of the trial are often not carried out by their research physicians or by personnel with significant expertise. Consequently, the quality of the patients randomly allocated to studies has not necessarily been optimal, as is the case for the follow-up. This can be worsened by pressure to enrol, originating either from the study centre because of financial considerations, or from the sponsors who want their study to be completed in the shortest possible time. For instance, it would be easy to enter into a trial for depression an

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individual with significant psychosocial difficulties who presented with a dysphoric mood and associated symptoms for the minimal duration of 4 weeks. The favourable reaction of such a person during a trial because of the resolution of his/her "environmental" problem(s), or because of the frequent contact with the treating team, would contribute to decreasing the signal-to-noise ratio in the study. As an analogy, a study examining the treatment of streptococcal pharyngeal infections with a novel antibiotic would be doomed to failure if the diagnosis were made uniquely on the hyperemic appearance of the patients' throats. Unfortunately, depression is still diagnosed using several signs and symptoms without biologic tests to help ascertain the presence of the illness.

There are several examples of medications for which clinical development was terminated because of failed, not negative, trials. The selective and potent noradrenergic reuptake inhibitor atomoxetine was shelved for several years in the early 1990s after it failed to separate from placebo in a large multicentre trial for depression. The tricyclic antidepressant desipramine also did not separate from placebo in that study. It has recently been introduced for the treatment of attention-deficit disorder in the United States. After using it off-label for depression in adults, I found it to be a useful and effective antidepressant, either in monotherapy or as an augmentation strategy, as expected from its pharmacologic profile.[3] The development of substance P receptor antagonists has also been impaired by a large number of failed studies, with active comparators not separating from placebo. Other novel agents with multiple neurochemical properties of the drug combinations that have proved effective in treatment-resistant depression have also been abandoned because of high placebo responses.

Given the heterogeneity of the clinical presentations of major depression and, in all likelihood, of its pathophysiology as well, it is unlikely that a single agent will ever be effective in all depressed patients. With placebo response rates of short-term studies sometimes being in the 50% range, the odds of identifying an antidepressant effect in global populations of patients with depression, for a drug that may have otherwise been very effective in subgroups of patients, are often slim. Strategies aimed at decreasing the placebo response are beyond the scope of this editorial. It is important, however, to emphasize that antidepressants remain extremely useful in the long-term treatment of depression and that the development of agents with novel mechanisms of action, even if not superior in effectiveness to the current ones, is still eagerly awaited for maximal patient comfort and optimal compliance.

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References

1. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. *Arch Gen Psychiatry* 2000;57(4):311-7.

2. Montgomery SA, Roberts A, Patel AG. Placebo-controlled efficacy of antidepressants in continuation treatment. *Int Clin Psychopharmacol* 1994;9(Suppl 1):49-53.

3. Brunello N, Blier P, Judd LL, Mendlewicz J, Nelson CJ, Souery D, et al. Noradrenaline in mood and anxiety disorders: basic and clinical studies. *Int Clin Psychopharmacol* 2003;18(4):191-202.