

**EVIDENCE-BASED MEDICINE**

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# Simple Options for Improving Signal Detection in Antidepressant Clinical Trials

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**ABSTRACT** ~ **Objective:** Previous experience with antidepressant studies highlight the difficulties in discriminating an effective drug from placebo. In hopes of improving signal detection, three easy-to-implement methodologies were employed during the development of a recently approved antidepressant. **Experimental Design:** Results from alternative and traditional methods could be compared directly because most studies employed both methods. This database included 11 double-blind, placebo-controlled trials (some with multiple dose arms and/or active comparators) yielding 22 treatment arms of antidepressants at or above the minimally effective dose noted in their U.S. labels. **Principal Observations:** Results agreed with the previous evidence showing that the performance of a likelihood-based, mixed-effects model repeated measures (MMRM) analysis was superior to that of analysis of covariance with missing values imputed using the last observation carried forward (LOCF) approach; MMRM correctly identified drug as superior to placebo in 14/22 (63.6%) comparisons versus 11/22 (50.0%) for LOCF. In agreement with previous studies, use of subscales of the Hamilton Depression Rating scale (HAMD) improved signal detection compared to the HAMD total score. Using MMRM with HAMD subscales correctly identified drug as superior to placebo in up to 17/22 (77.3%) comparisons. Excluding double-blind, placebo lead-in responders did not increase the frequency of correctly identifying drug-versus-placebo differences. **Conclusions:** The 22 drug-versus-placebo comparisons in this report offer a small amount of evidence and therefore may not be convincing on their own, although results do agree with previous research. Researchers may be able to take advantage of these easy-to-implement methods while we wait for further improvements in other areas. *Psychopharmacology Bulletin. 2007;40(2):101-114.*

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## INTRODUCTION

Signal detection is often thought of as the ability to detect a treatment as effective, when it is effective. Recent evidence illustrates that considerable room for improvement in signal detection exists for both drugs in general and antidepressants in particular. For example, consider the following statistics on drug development in the U.S. presented by Dr. John Jenkins, Director of the Office of New Drugs at the U.S. Food and Drug Administration (FDA), at the International Conference on Drug Development, February 25, 2004: Less than 20% of the compounds entering Phase II testing receive regulatory approval, and less than 50% of the compounds entering Phase III receive regulatory approval. In addition, Khan et al.<sup>1</sup> compiled a database from FDA summary bases of approval for all antidepressants approved between 1985 and 2000; less than half of the comparisons of these known effective antidepressants yielded significant differences from placebo. Such results imply an unduly high rate of false positive and false negative findings in clinical trials, which would contribute to inefficiency in drug development.

Khan et al.<sup>2</sup> noted several design factors and patient characteristics that were associated with likelihood of success in antidepressant clinical trials: flexible (as compared with fixed) dosing, greater illness severity at baseline, fewer treatment arms, and lower percentage of female patients. However, making use of these historical associations in improving signal detection in future trials requires important trade-offs. For example, flexible dosing may improve signal detection, but it also reduces the ability to assess dose response. Moreover, it is not entirely clear that altering designs in accordance with the historical associations will have the desired effect. For example, increasing minimum baseline severity for trial entry will create a study sample more severely ill at baseline, but it also makes patient recruitment more difficult, thereby increasing the enrollment period and/or potentially increasing the tendency to inflate baseline scores or to enroll patients that should otherwise be excluded as investigative sites try to meet enrollment timelines. Hence, while the findings of Khan et al.<sup>2</sup> are an important step in understanding antidepressant clinical trials and in designing better trials, other approaches need to be considered.

Research has suggested several easy-to-implement methods may also improve signal detection for antidepressants and may not involve important trade-offs. The objectives of the present article are to review the research supporting of these three approaches for improving signal detection for antidepressants and assess the benefits of these methods in the development programs of a recently approved antidepressant. The three approaches are as follows: 1) choosing the primary analysis, 2) choosing the primary outcome measure, and 3) excluding patients

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with large responses during double-blind placebo lead-in periods from the primary analysis.

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