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Antidepressant Signal Detection in the Clinical Trials Vortex

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Vortioxetine (Lu AA21004) is a novel antidepressant medication approved at doses of 10–20 mg/d for the treatment of major depressive disorder (MDD) by the US Food and Drug Administration (FDA) in September 2013 and by the European Commission in December 2013. This issue of the *Journal* includes reports of 2 clinical trials conducted exclusively in the United States that evaluated the efficacy and safety of vortioxetine versus placebo for the treatment of MDD. The 2 trials were similar in design and used 3 treatment arms: placebo and 2 vortioxetine doses (10 and 20 mg/d in the study by Jacobsen and colleagues[1] and 10 and 15 mg/d in the study by Mahableshwarkar and colleagues[2]). In the Jacobsen et al trial, the 20-mg/d dose achieved superiority (a finding replicated in a second, as yet unpublished, US trial),[3] but in the Mahableshwarkar et al trial, neither dose statistically separated from placebo on the primary outcome. Two prior published US trials comparing a 5-mg/d dose versus placebo also failed to demonstrate superiority of vortioxetine.[4,5] These results contrast sharply with prior trials conducted outside the United States, in which 5- and 10-mg doses demonstrated efficacy over placebo in adults with MDD,[6–8] and 1 trial in which vortioxetine 10–20 mg/d proved superior to agomelatine in treatment-resistant MDD.[9]

The Mahableshwarkar et al and Jacobsen et al trials did not include an active comparator arm. Thus, we cannot conclude whether the failure of vortioxetine at 10–15 mg/d to separate from placebo represents a "failed trial" or a "negative trial." Four prior published trials of vortioxetine for MDD used an active comparator (venlafaxine XR or duloxetine), resulting in 1 negative US trial,[5] 1 failed ex-US trial,[7] and 2 positive trials.[6,10]

The conflicting results of the vortioxetine trials raise again an important question for researchers, regulators, and the pharmaceutical industry: Why do trials using the same drug and similar designs fail to agree with one another? Roughly half of the trials of compounds receiving FDA approval for antidepressant use failed to demonstrate superiority over placebo.[11] Although some of these negative trials employed doses later determined to be below the minimum efficacious dose, the problem remains salient. These inconsistent results greatly increase the cost of drug development and diminish the public's confidence that psychiatric treatments are any better than placebo.[12]

The sources of variability in outcomes for clinical trials of psychiatric medications can be divided into 3 broad categories: trial design characteristics, study participant characteristics, and quality of study conduct. Other than for dose differences, the Jacobsen et al and Mahableshwarkar et al trial designs were similar to all prior published placebo-controlled vortioxetine treatment trials for MDD: a 6–8 week treatment duration in adults with recurrent, at least moderately severe, depression who had failed to respond to no more than 1 antidepressant in the current episode. Although there was some minor variability in the baseline minimum symptom severity thresholds required for inclusion, this factor did not appear to affect trial outcome. Thus, it is very unlikely that the observed differences in outcomes can be explained by study design characteristics. Rather, differences in outcomes must arise from either (1) the conduct of the study procedures or (2) characteristics of the enrolled study participants.

Potentially important sources of inconsistency of study procedures between sites include the level of rigor in application of inclusion/exclusion criteria, quality and consistency of rating scale assessments, and the degree of emotional support and advice provided to participants by the study staff.[13] Attempts to improve the accuracy and precision of severity ratings include the use of centralized raters, who are remote from the site and masked to the design of the trial, as well as the use of computer ratings and interactive voice response technology to rate symptom severity.[14,15] Some data support the use of these measures in improving signal detection.[16,17] Although centralized raters were used in the Mahableshwarkar et al trial, the vortioxetine arms did not separate from placebo.

Historically, the greatest concern about study participant samples has been their degree of responsiveness to placebo. Most negative and failed trials of proven antidepressants have occurred in studies that produced a high rate of placebo response; strong response to placebo creates a ceiling effect that leaves the active drug with little room to demonstrate efficacy. A meta-analysis of antidepressant trials revealed that studies with placebo response rates ≤ 30% provide the best chance for demonstrating superiority of an investigational drug.[18] However, in the Mahableshwarkar et al and Jacobsen et al trials, in which the 10-mg/d dose failed to demonstrate superiority, the placebo response rates were only 28.4% and 32.9%, respectively. In contrast, in the positive Alvarez et al ex-US trial, the placebo response rate was 45%.[6]

What can explain these poorer vortioxetine outcomes in trials with lower placebo response? The most likely source of variability in trial outcomes lies in differences in the sample populations enrolled. MDD is a heterogeneous illness, but there is little reason to think that the populations with MDD in the United States are any more or less likely to respond to antidepressant medications than those from outside the

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United States. Indeed, the recent trend for US-conducted trials to show poorer drug-placebo separation is a reversal of the generally better signal detection that occurred in US trial sites through the 1980s and 1990s.[3] In the vortioxetine trials, the sponsor's analysis found that the mean body mass index in the US trials was higher than those of European sites, but body mass index was not a moderator of outcome across the trials.[3] The most likely conclusion is that patients enrolling in recent clinical trials in the United States differ from non-US and older US samples on 1 or more unmeasured confounding variables.

The level of socioeconomic deprivation of participants in MDD trials may be an important source of variance. A growing body of evidence indicates that poor and chronically unemployed patients are unlikely to respond to standard treatments for MDD (including psychotherapy) compared to patients with greater economic security.[19–21] Patients living in an environment of socioeconomic deprivation, and with few opportunities to experience emotional reward, have depressive symptoms that are unlikely to be impacted by pharmacologic mechanisms. In the United States, these are often the patients who lack easy access to mental health care and thus enroll in clinical trials. Indeed, the low response rates to both placebo and active drug suggest that such participants comprised a significant proportion of the US trials. Thus, the vortioxetine trials published here may represent a new problem with clinical trial samples: patients with very low likelihood of any response may threaten the validity of the trial. Future trials may want to include a measure of individual socioeconomic deprivation such as the New Zealand Index of Socioeconomic Deprivation for Individuals (NZiDeP)[22] and conduct subgroup analyses to evaluate its impact on outcomes.

Another cause for concern about the characteristics of the enrolled participants in the Mahableshwarkar et al[2] trial was the slow rate of recruitment and subsequent decision to increase the number of trial sites from 35 to 65. Greater numbers of trial sites,[23] non-academic sites,[24] and rapid on-boarding of additional sites[25] and patients[26] in order to enhance recruitment have been associated with MDD trial failure. Sites that enroll rapidly sometimes employ databases of subjects who have participated in prior trials and are willing to enter another. Use of site-based participant databases (which is often a requirement for selection as a site) may be a concern, particularly when trials, like these vortioxetine trials, exclude treatment-resistant patients. The condition of a subject who is willing and able to wait to participate in a clinical trial may be very different from that of a patient in the community who is actively seeking care. (In the US vortioxetine trials, 32 participants were *concurrently* enrolled in more than 1 vortioxetine study.[27]) How placebo- and drug-responsiveness differs in database-identified subjects versus de novo recruited subjects is certainly worthy of exploration.

Finally, an additional but often overlooked way in which subject heterogeneity complicates clinical trial results relates to its impact on the inferential statistical approaches commonly employed to analyze trials. There is an inherent assumption that the subject population is appropriately representative of the larger population of patients with a specific disorder and that each trial contains approximately the same number of subjects whose syndrome, in this case MDD, is caused by the same pathophysiologic processes. Although it is statistically easier to design clinical trials employing these assumptions, they may greatly limit our ability to appreciate the efficacy of a compound for an important subgroup of patients. A growth mixture modeling analysis of the Lilly duloxetine trials for MDD demonstrated that there was substantial heterogeneity in response to duloxetine, with one group of subjects demonstrating marked improvement with duloxetine treatment, while a second group of subjects became significantly more symptomatic with duloxetine treatment.[28]

Determining the true minimum effective dose for vortioxetine has important implications for understanding its mechanism of action. In addition to inhibiting the serotonin transporter (SERT), vortioxetine acts as an antagonist at 5-HT_{1D}, 5-HT_3, and 5-HT_7 receptors; is a partial agonist at 5-HT_{1B} receptors; and is an agonist at 5-HT_{1A} receptors. While these various actions suggest possible therapeutic benefits beyond SERT blockade, they may also lead to greater uncertainty and inconsistency of the drug effects between individuals. Antidepressant efficacy for SSRIs is believed to require blockade of 70%–80% of the SERT in the dorsal raphe[29]; for vortioxetine, this level of inhibition requires doses in the 20–30 mg/d range.[30] The efficacy of vortioxetine at doses < 20 mg/d in ex-US trials suggests that the non-SERT mechanisms contribute to its antidepressant effect, whereas the US trials suggest that the typical SSRI level of SERT blockade is required for vortioxetine's efficacy. Time will tell whether the US or ex-US trials better represent the true antidepressant dose effects.

Taken together, the vortioxetine studies demonstrate the challenges we face in generating reliable data from clinical trials. Although the double-blind, randomized trial remains the gold standard to test drug efficacy, advancements to improve consistency across similarly designed trials are needed.

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