

US Food and Drug Administration's Review of the Novel Antidepressant Vortioxetine

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The article by Zhang and colleagues¹ in this issue of *The Journal of Clinical Psychiatry* provides a concise summary of the evidence reviewed by the US Food and Drug Administration (FDA) as part of its evaluation of the novel antidepressant vortioxetine. The article also offers some insights into the FDA's decision-making process that led to the drug's approval and their recommendations for further studies. Approved by the FDA in September 2013 for treatment of episodes of major depressive disorder, vortioxetine is one of the newer options available for this important area of therapeutics. Although the material reviewed in this article can be examined in more detail on the FDA's website,² it is quite valuable to have this abridged, clinician-friendly review article. With these benefits in mind, it is hoped that similar reviews will be prepared to accompany the introduction of each subsequent new psychotropic compound.

As the FDA is the legally designated gate keeper for new US medications, we can assume when a new antidepressant reaches the US market that there is evidence of efficacy and that it is "safe enough." For antidepressants, the FDA has long defined efficacy by at least 2 positive randomized controlled trials (RCTs) and, ideally, a "preponderance of evidence" in comparison to existing standards. Safety is likewise gauged against placebo and existing standards, though it is acknowledged that postmarketing surveillance is necessary to fully explicate the risks of rare side effects. The FDA review of vortioxetine underscores that, as compared to other recently launched antidepressants, an unusually large amount of data from placebo-controlled RCTs is already available. The review of Zhang et al¹ includes data from 11 relevant RCTs—9 acute phase trials in adults (aged 18–75 years), 1 acute phase trial in elders (aged 64 years and older), and 1 longer term, recurrence prevention study. Six of the acute phase studies employed an active comparator (5 studies employed duloxetine and 1 study used venlafaxine). Thus, given the amount of evidence from phase 2 and phase 3 studies, the number of controlled trials of vortioxetine at the time that the drug was launched was at least double what is usually available at the time a drug is launched. As 7 of these 11 RCTs were judged by the FDA reviewers to be positive trials, there is little doubt about the antidepressant efficacy of vortioxetine.

One must read between the lines to deduce that the reason that such a large number of studies have been performed was an unanticipated regional difference in vortioxetine's dose-response performance. Specifically, whereas the 5- and 10-mg/d doses of vortioxetine were significantly more effective than placebo throughout most of the world, the 5-mg dose was not found to be effective in 2 studies conducted in the United States. A second wave of studies was therefore undertaken to determine if higher doses (ie, 15–20 mg/d) were effective in the United States. Following completion of this second group of RCTs, the FDA concluded that 20 mg/d was indeed an effective dose in the United States, whereas outside of the United States, it can be said with reasonable confidence that vortioxetine shows an ascending dose response curve from 5 to 20 mg/d.

Do people in the United States really need to take 4 times as much of this medication to get a therapeutic response? Of course not—the observed differences in efficacy almost certainly pertain to problems with signal detection in contemporary RCTs of antidepressants, which, in the case of the studies of vortioxetine, was more evident in the United States than elsewhere in the world. This has not always been the case; as noted by Zhang et al,¹ the results of an earlier meta-analysis of regulatory submissions across several decades concluded that signal detection used to be better in studies conducted within the United States.³ However, an opposite pattern was evident in the registration studies of vortioxetine, a point that was nicely illustrated by the findings of the study⁴ conducted in late-life depression. This study recruited about one-third of its sample in the United States, which facilitated comparison of outcomes among the patients recruited in the United States versus those enrolled elsewhere. The investigators found that the 5-mg/d dose was indeed effective in the subset of non-US patients, but not in the US subsample. Moreover, the active comparator—duloxetine 60 mg/d—also showed a much larger effect in the subsample recruited outside of the United States than in the US patients.⁴

Looking across studies, doses, and regions, vortioxetine likewise shows an ascending dose-response relationship for tolerability.¹ Thus, as one advances the dose in pursuit of a stronger antidepressant effect, it is more likely that treatment will be adversely affected by side effects. With this caveat in mind, the FDA recommendation to aim for the 20-mg/d dose for maximum efficacy but to consider lower doses for patients who have difficulties tolerating higher doses appears to make perfect sense for US practitioners.

So, beyond dose-response relationships and regional differences in study outcomes, what is really new about

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vortioxetine? Perhaps most interestingly, the FDA report describes vortioxetine as a selective serotonin reuptake inhibitor (SSRI), yet it acknowledges that this compound has a number of other receptor-mediated effects that may be relevant to central nervous system function in general and serotonergic neurotransmission in particular. The FDA review concludes that these “secondary” receptor effects have uncertain clinical relevance.¹ It is almost certain, for example, that vortioxetine does not have a stronger antidepressant effect than the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine.¹ However, Sanchez and colleagues⁵ marshal evidence to suggest that the receptor-mediated effects of vortioxetine—which include antagonism of 5-HT_{1D}, 5-HT_{3A}, and 5-HT₇ receptors; partial agonism of 5-HT_{1B} receptors; and agonism of 5-HT_{1A} receptors—may convey important differences in side effect profile (eg, fewer sexual side effects) and secondary therapeutic effects (eg, better effects on cognition) when compared to “purer” SSRIs such as escitalopram or the SNRI duloxetine. This difference in perspective is understandable, as the FDA uses a much higher standard to evaluate claims of superiority than is typical for people who are closely tied to a drug’s development.

With respect to sexual side effects, the FDA’s review concludes that, although the rate of spontaneous reports of sexual side effects with vortioxetine therapy is relatively low, it is greater than placebo. Further, when focusing on the subset of studies that used duloxetine as a comparator and included a prospective assessment of treatment-emergent adverse effects on sexual function, they saw no evidence of an advantage. Whether further studies using more sensitive designs, such as switching patients with a history of SSRI-related sexual dysfunction to either a second SSRI or vortioxetine, will show the hypothesized advantage remains to be seen.

The FDA review is silent on the proposed beneficial effects of vortioxetine on measures of cognitive function. At the time the review was undertaken, only a single relevant study was available,⁴ and the results of this study, though interesting, fell below the FDA’s threshold for superiority. It is therefore noteworthy that the results of a second prospective RCT,⁶ which were not available at the time of the FDA review,

indicated that vortioxetine has favorable effects on memory and executive cognitive function that are not explained as simple epiphenomena of antidepressant efficacy. Whether such effects are actually superior to those of SSRIs and SNRIs, and whether such effects are specifically explained by 1 or more of the receptor-mediated effects, will require another wave of more-focused research that may help to clarify whether vortioxetine represents a small or large incremental advance in the therapeutics of depressive disorders.

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