Journal of Affective Disorders 190 (2016) 357–361

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Inclusion/exclusion criteria in placebo-controlled studies of vortioxetine: Comparison to other antidepressants and implications for product labeling

Mark Zimmerman *, Heather L. Clark, Matthew D. Multach, Emily Walsh, Lia K. Rosenstein, Douglas Gazarian

Department of Psychiatry and Human Behavior, Brown Medical School, Rhode Island Hospital, Providence, RI, United States

ARTICLE INFO

Article history:
Received 15 July 2015
Received in revised form
29 September 2015
Accepted 22 October 2015
Available online 25 October 2015

Keywords:
Vortioxetine
FDA
Exclusion criteria
Antidepressant efficacy trials
External validity
Antidepressants
Generalizability

ABSTRACT

Background: We recently conducted a comprehensive review of the psychiatric inclusion/exclusion criteria used in 170 placebo-controlled antidepressant efficacy trials (AETs) published during the past 20 years and found that the criteria of more recent studies were significantly more restrictive than prior studies. Vortioxetine is the most recently approved medication for the treatment of major depressive disorder (MDD). We compared the inclusion/exclusion criteria of the vortioxetine studies to the criteria used in other AETs, and discuss the broader issue of the generalizability of AETs and the implications this might have for the labeling of antidepressants receiving FDA approval.

Methods: We conducted a comprehensive literature review of placebo-controlled AETs published from January, 1995 through December, 2014. We identified 170 AETs published during this 20 year period and compared the inclusion/exclusion criteria used in the 12 studies of vortioxetine to those used in the nonvortioxetine studies. A second analysis compared vortioxetine to the 3 antidepressants most recently approved prior to vortioxetine (desvenlafaxine, levomilnacipran extended release, vilazodone).

Results: Compared to the nonvortioxetine AETs, the vortioxetine studies significantly more often excluded patients with any comorbid Axis I disorder ($p < .001$) and more often required the current depressive episode to be longer than the DSM minimum symptom duration requirement of 2 weeks ($p < .01$). The cutoff on the Montgomery Asberg Depression Rating Scale required for inclusion in the vortioxetine studies was higher than the cutoff used in the other AETs ($p < .01$).

Limitations: A limitation of the present analysis is that it was based on published placebo-controlled studies of antidepressants.

Conclusion: The inclusion/exclusion criteria in the studies of vortioxetine were more restrictive than the criteria used in other AETs. Inconsistent with FDA guidelines on the labeling of medications, the label of vortioxetine does not include a description of the limits to the group of patients with MDD for whom the medication has been shown to be effective.

1. Introduction

More than a decade ago our clinical research group raised questions about the generalizability of antidepressant efficacy trials (AETs) because the majority of patients with major depressive disorder (MDD) presenting for treatment to our outpatient practice would not have met the inclusion/exclusion criteria of a typical study (Zimmerman et al., 2002). Subsequent studies replicated this finding (van der Lem et al., 2011; Wisniewski et al., 2009; Zetin and Hoepner, 2007). We also conducted a brief literature review of 39 AETs published in 5 journals over a 6 year period and found that several criteria such as the presence of suicidal ideation, substance use disorder, and low scores on symptoms severity measures were used to exclude patients in the majority of studies (Zimmerman et al., 2004).

We recently updated and expanded this literature review and conducted a comprehensive review of the psychiatric inclusion/exclusion criteria used in 170 placebo-controlled AETs published during the past 20 years (Zimmerman et al., 2015). We compared the inclusion/exclusion criteria of studies published during the past 5 years (2010–2014) to those of the prior 15 years (1995–2009) and found that the criteria were significantly more restrictive for study inclusion in the more recent studies.

* Correspondence to: 146 West River Street, Providence, RI 02904, United States. Fax: +1 401 444 7107.
E-mail address: mzimmerman@lifespan.org (M. Zimmerman).

http://dx.doi.org/10.1016/j.jad.2015.10.041
0165-0327/

Vortioxetine is the most recently approved medication for the treatment of major depressive disorder (MDD). A recent article described the United States' Food and Drug Administration's (FDA) perspective on the medication's approval (Zhang et al., 2014). Zhang and colleagues reviewed the data submitted to the FDA on the medication's efficacy and safety, and then discussed three major issues in the approval decision— mechanism of action, dose determination related to regional difference, and sexual dysfunction. One of the issues barely addressed was the extent to which the patients in the FDA-reviewed studies may or may not have been representative of patients seen in routine clinical practice.

In the present report we compared the inclusion/exclusion criteria of the vortioxetine studies to the criteria used in other AETs, and discuss the broader issue of the generalizability of AETs and the implications this might have for the labeling of antidepressants receiving FDA approval.

2. Methods

We reviewed the tables of contents of 49 journals from January, 1995 through December, 2014 to obtain a comprehensive set of placebo-controlled AETs. The journals reviewed were those that had published studies included in prior comprehensive reviews of placebo-controlled AETs (Papakostas and Fava, 2009; Undurraga and Baldessarini, 2012). This was supplemented with a search of the Medline (via PubMed), EMBASE (via Ovid), and PsychINFO (via Ebsco host) databases for the same time period. We used the search terms "depression" or "depressive" and "placebo". Only articles published in English were included. We also examined the reference lists of meta-analyses of AETs, and the studies identified from our literature review. Eight recent meta-analyses or reviews of vortioxetine were examined (Al-Sukhni et al., 2015; Berhan and Barker, 2014; Fu and Chen, 2014; Garnock-Jones, 2014; Meeker et al., 2015; Pae et al., 2015; Sanchez et al., 2015; Tritschler et al., 2014).

We did not include trials that focused on refractory depression, chronic depression, bipolar, psychotic, atypical or melancholic subtypes of depression, trials focused on depressed patients with particular symptoms such as anxious features, trials based on inpatient samples, or trials limited to patients with a particular comorbid condition such as alcoholism, anxiety disorder, or medical illness. We only included trials focused on patients with MDD, and therefore did not include trials that were based on an admixture of patients with MDD, dysthymic disorder, and minor depression. The inclusion of a small number of patients with bipolar depression was not the basis for excluding the trial from our review, though trials limited to patients with bipolar disorder were not included. Trials resulting in multiple publications based on the same sample (and the same set of inclusion/exclusion criteria) were included only once. We did not include trials of intravenous or injectable forms of medication, and also did not include trials of medication combinations or augmentation strategies. We included trials whether or not the medication had received regulatory approval for the treatment of depression.

Two of the authors independently reviewed each article and completed a form listing the psychiatric inclusion and exclusion criteria used in the study. The reviewers met, compared the results of their data abstraction, and resolved discrepancies.

2.1. Data analyses

We identified 170 AETs published during the past 20 years. Subsequent to our review 2 additional placebo-controlled studies of vortioxetine were published, and 1 unpublished study accessed through clinicaltrials.gov was identified in the meta-analyses of vortioxetine. Each of these 3 studies were added to our data base. We compared the 12 studies of vortioxetine (Alvarez et al., 2012; Baldwin et al., 2012; Boulenger et al., 2014; Henigsberg et al., 2012; Jacobsen et al., 2015; Jain et al., 2012; Katona et al., 2012; Mahableshwarkar et al., 2013, 2015a, 2015b; McIntyre et al., 2014; Takeda, 2013) to the remaining 161 studies on the psychiatric inclusion/exclusion criteria that we identified in our earlier publication (Zimmerman et al., 2004), as well as 4 criteria that we did not examine in the earlier report (previous suicide attempt, homicidal/violence risk, severity scale score above cutoff, exclusion if any Axis I disorder is present). We had previously combined the exclusion of depressive episodes that were either too long or too short, whereas in the current analysis we listed these separately. In a secondary analysis we compared the 12 vortioxetine trials to the 23 trials of the 3 antidepressants most recently approved prior to vortioxetine (desvenlafaxine, levomilnacipran extended release, vilazodone) (Asnis et al., 2013; Bakish et al., 2014; Boyer et al., 2008; Clayton et al., 2013; Clayton et al., 2015; Croft et al., 2014; DeMartinis et al., 2007; Dunlop et al., 2011; Feiger et al., 2009; Gommoll et al., 2014; Iwata et al., 2013; Khan et al., 2011; Kornstein et al., 2010; Lieberman et al., 2008; Liebowitz et al., 2008', 2013', 2007; Mathews et al., 2015; Montgomery et al., 2013; Rickels et al., 2009; Sambunaris et al., 2014; Septien-Velez et al., 2007; Tourian et al., 2009). The groups were compared by the chi-square statistic, or by Fisher's Exact Test if the expected value in any cell of a 2×2 table was less than 5. Because of the multiple comparisons between groups we used an alpha level of .01 to indicate statistical significance.

3. Results

All 12 vortioxetine studies excluded patients with any comorbid Axis I disorder, vs. less than one-quarter of all other AETs ($p < .001$) (Table 1). Each of the studies of vortioxetine excluded patients with borderline personality disorder or dysthymic disorder, in contrast to a minority of the nonvortioxetine studies (Table 1). All vortioxetine studies required the current depressive episode to be longer than the DSM minimum symptom duration requirement of 2 weeks (Table 1). Eleven of the 12 vortioxetine studies required a minimum duration of 3 months, and 1 study of elderly patients a minimum duration of 1 month (Katona et al., 2012).

Every AET required a minimum score on a symptom severity scale, usually the Hamilton Depression Rating Scale (Hamilton, 1960) or the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). All studies of vortioxetine required a minimum score on the MADRS. The cutoff on the MADRS required for inclusion in the vortioxetine studies was higher than the cutoff used in the 26 nonvortioxetine studies which used the MADRS, with all but one of the vortioxetine studies using a cutoff above 25 in contrast to less than one-third of the other studies (91.7% vs. 30.8%, $\chi^2 = 12.2$, $p < .01$) (Table 2).

In a secondary analysis we compared the inclusion/exclusion criteria of the 12 trials of vortioxetine to the 23 published trials on desvenlafaxine ($n = 14$), levomilnacipran extended release ($n = 5$), and vilazodone ($n = 4$) on the variables noted above that significantly distinguished the vortioxetine and nonvortioxetine studies. Significantly more of the vortioxetine trials excluded patients with any Axis I disorder (100.0% vs. 8.7%, Fisher's Exact Test = .000). Another 5 nonvortioxetine studies excluded patients with any Axis I disorder except generalized anxiety disorder, social phobia, and specific phobia. If these studies are counted as excluding patients with any Axis I disorder then the difference was still significant (100.0% vs. 30.4%, $\chi^2 = 15.4$, $p < .001$). The vortioxetine trials were not significantly more likely to require a