# Vortioxetine Versus Placebo for Major Depressive Disorder: A Comprehensive Analysis of the Clinical Trial Dataset

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## ABSTRACT

***Objective:*** To conduct a meta-analysis of studies of vortioxetine in adults with major depressive disorder (MDD).

***Data Sources:*** Abstracts were identified using PubMed by cross-referencing *vortioxetine* with *placebo* and *randomized*. No language or publication year restrictions were used.

***Study Selection:*** Randomized, double-blind, placebo-controlled clinical trials comparing oral vortioxetine monotherapy with placebo for acute treatment of MDD.

***Data Extraction:*** Data were extracted with a pre-coded form, as follows: number of patients randomized, treatment group, Montgomery-Asberg Depression Rating Scale (MADRS) response and remission rates, and mean change in scores from baseline and standard errors for the MADRS, Hamilton Anxiety Rating Scale (HARS), and Digit Symbol Substitution Test (DSST).

***Results:*** 7,269 subjects randomized to vortioxetine (n = 3,630) or placebo (n = 3,639) from 17 studies were included. The probability of receiving placebo did not predict difference in change in MADRS scores between vortioxetine and placebo (estimate = 4.1, $P = .54$). The standardized mean difference (SMD) (95% CI) for change in MADRS score for vortioxetine overall versus placebo was 0.33 (0.24 to 0.41) and was 0.24 (0.08 to 0.39), 0.33 (0.19 to 0.47), 0.26 (−0.06 to 0.58), and 0.44 (0.27 to 0.62) for 5-mg, 10-mg, 15-mg, and 20-mg doses, respectively. Greater difference in efficacy between drug and placebo was observed in studies with a low rather than a high placebo response rate.

***Conclusions:*** Vortioxetine is more effective than placebo in improving depression, anxiety, and cognition. Less informative or uninformative studies obscured the true treatment effect.

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Major depressive disorder (MDD) is one of the most common and deleterious illnesses to affect humankind, posing several unique challenges to clinicians and patients alike.[1–9] Vortioxetine was approved by the US Food and Drug Administration (FDA) for treatment of MDD in 2013.[10] It differs from commonly used serotonin reuptake inhibitor antidepressants in its multimodal mechanism of action as it is a serotonin (5-HT) reuptake inhibitor, a 5-$HT_{1A}$ receptor agonist, a 5-$HT_{1B}$ partial agonist, and a 5-$HT_3$, 5-$HT_{1D}$, and 5-$HT_7$ receptor antagonist.[11] In clinical trials to date, vortioxetine has been shown to improve symptoms of depression[12–14] along with performance on objective measures of cognition.[15–18]

When making treatment choices, it is critically important that clinicians and patients have a clear understanding of the extent (across symptoms) and degree of efficacy of each available treatment. Previous meta-analyses of vortioxetine have focused on symptomatic improvements[19–27] or changes in cognitive function (such as those measured by the Digit Symbol Substitution Test [DSST])[15] and involved pooling all available data existing at the time. These prior meta-analyses yielded evidence of efficacy for vortioxetine in depression. The purpose of the present work was to build upon previous analyses to include newer studies, but also to broaden and deepen our understanding of the efficacy of this compound across symptoms and according to individual study performance. To do so, we compiled all data from randomized, placebo-controlled trials of vortioxetine in MDD and applied 3 key lessons learned from our previous work: (1) that different starting doses can have differential efficacy,[28] (2) that the probability of being randomized to placebo can influence the drug effect size,[29] and (3) that a greater degree of improvement over time in the placebo group is related to a smaller difference in efficacy between drug and placebo.[30] The scope of our investigation included the Montgomery-Asberg Depression Rating Scale (MADRS),[31] Hamilton Anxiety Rating Scale (HARS),[32] and the DSST.[33]

**Clinical Points**

- Previous meta-analyses have shown vortioxetine to be efficacious in treating depressive symptoms, but have offered limited information on the differential effects of different doses.
- Vortioxetine is effective in treating depression, anxiety, and cognitive symptoms.
- Placebo responders may have led previous studies to underestimate the efficacy of vortioxetine.

## METHODS

### Data Sources and Search Strategy

Studies were first identified using searches of PubMed on April 23, 2020. Searches were conducted by cross-referencing the term *vortioxetine* with the terms *placebo* and *randomized*. No language or year-of-publication restrictions were used. At the time of submission, we have not identified any further studies meeting our inclusion criteria published since the date of our initial search.

### Study Selection

We selected randomized, double-blind, placebo-controlled clinical trials comparing oral vortioxetine monotherapy with placebo for the acute treatment of MDD. We then selected studies that also met all of the following inclusion criteria:

1. Studies that used the MADRS[31]
2. Studies that exclusively focused on patients with MDD.

Reports were excluded if they exclusively focused on the treatment of patients with remitted or partially remitted MDD, bipolar disorder, dysthymic disorder, psychotic MDD, minor depressive disorder, or seasonal affective disorder or of depressed patients with a specific medical condition or active alcohol or substance abuse disorders. Reports not describing original data (ie, containing data published elsewhere) and those that were not focused on the acute phase of treatment (ie, continuation, maintenance, relapse prevention) were excluded.

### Data Extraction

Data were extracted with the use of a pre-coded form. The following data were extracted from trials included in the study: the number of patients randomized to each treatment arm, treatment group (vortioxetine dose versus placebo), MADRS response rates, MADRS remission rates, and mean change in scores from baseline and their corresponding standard errors for the MADRS, the HARS, and the DSST.

Data were extracted by one of the authors and checked for accuracy by the others, and any discrepancies were resolved in a joint meeting when compiling the final dataset. Missing data were obtained either by the study report posted on ClinicalTrials.gov or by directly contacting the sponsor. For clinical relevance, our analysis focused only on FDA recommended dose levels of vortioxetine (5–20 mg).

### Quantitative Data Synthesis

Random-effects meta-analysis was utilized to estimate continuous (change in symptom score over time) and dichotomous (response and remission rates) effect sizes between treatment groups (vortioxetine and placebo). Two separate meta-regressions were utilized to investigate the correlation between either (1) the change in MADRS scores in the placebo group or (2) the probability of receiving placebo in the study (independent variable) with the difference in MADRS mean change between the two treatment groups (dependent variable). We then calculated the (study-level) median change in MADRS scores for patients receiving placebo among all studies. We repeated all analyses and limited them to the subset of studies with a change in MADRS score over time in patients receiving placebo who demonstrated a mean change that was below the group median for all studies. All analyses utilized the meta package of meta-analytic tools as implemented in Stata 15 (StataCorp LLC; College Station, Texas).

## RESULTS

Ninety-seven abstracts were identified with the use of PubMed. Of these, 75 were excluded because they did not describe eligible studies (open-label studies, reviews, meta-analyses, post hoc analyses, studies of healthy subjects, or studies of other disorders). Two focused on the adjunctive use of vortioxetine in MDD and were thus excluded.[34,35] Two were excluded because they focused on the use of vortioxetine in remitters or near-remitters with MDD.[36,37] One was excluded because the focus was on maintenance and not on acute therapy for MDD with vortioxetine.[38] The remaining 17 studies were found eligible and included in the analysis.[12–14,16,39–51] A PRISMA flow diagram of this information is shown in Figure 1.

These trials and some of their characteristics are outlined in Table 1. All identified studies used the MADRS as an outcome measure. All data points were available for all trials and were pooled. In summary, the pooled dataset involved a total of 7,269 subjects randomized to vortioxetine (n = 3,630) or placebo (n = 3,639). The median MADRS score change in the placebo group was −12.37. The first meta-regression conducted did not identify the probability of receiving placebo to predict the difference in change in MADRS scores between vortioxetine and placebo (estimate = 4.1, $P = .54$). The second meta-regression did identify the degree of change in MADRS scores in the placebo group to predict the difference in change in MADRS scores between vortioxetine and placebo (estimate = −0.066, $P = .002$). The SMD (95% CI) for change in MADRS score versus placebo was 0.33 (0.24 to 0.41) overall and was 0.24 (0.08 to 0.39), 0.33 (0.19 to

**Figure 1. PRISMA Flow Diagram**

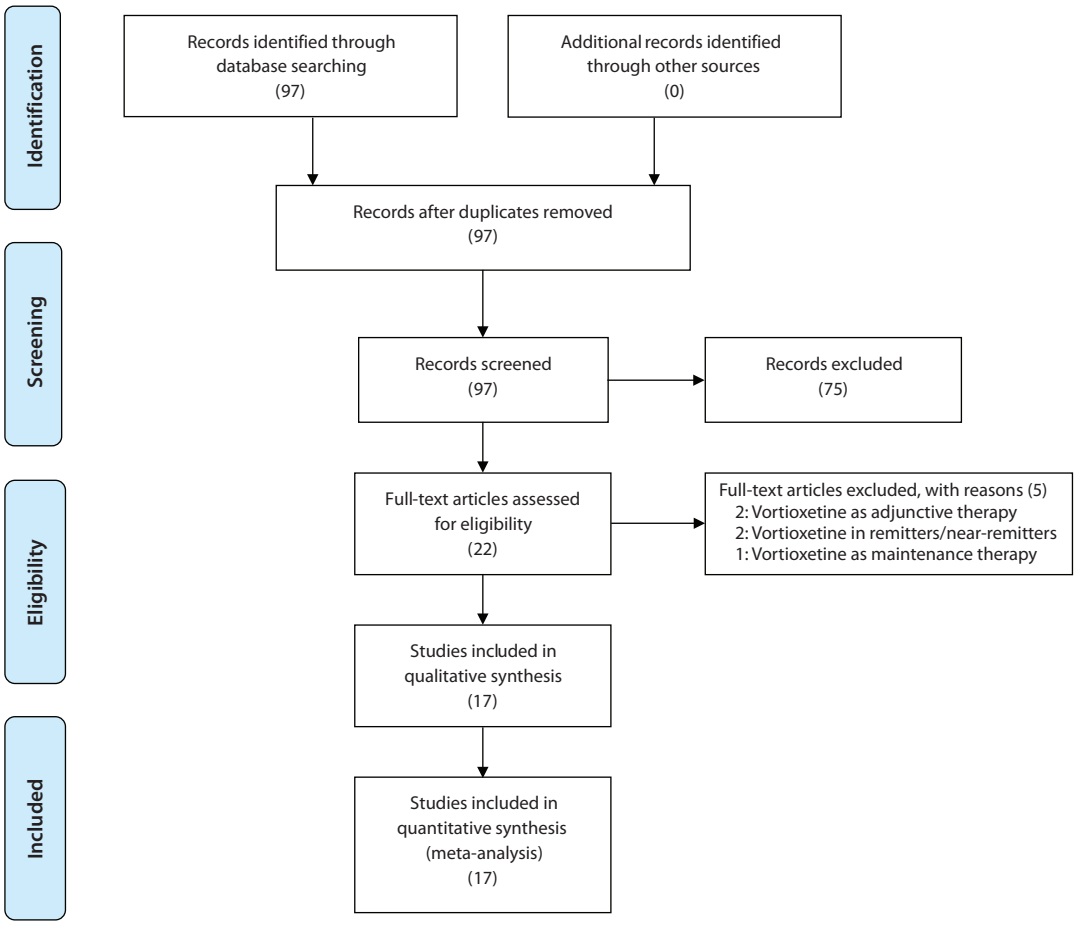



**Table 1. Studies Pooled and Their Characteristics**

| References | MADRS | HDRS | HARS | DSST | 5 mg | 10 mg | 15 mg | 20 mg | MADRS mean change, placebo | Probability, placebo |
|---|---|---|---|---|---|---|---|---|---|---|
| Baldwin et al, 2012[39] | x | x | X | | N | N | | | −14.8 | 0.2 |
| Mahableshwarkar et al, 2013[40] | x | x | X | | N | | | | −14.8 | 0.2 |
| Jain et al, 2013[41] | x | x | X | | N | | | | −11.22 | 0.25 |
| Henigsberg et al, 2012[42] | x | x | X | | P | P | | | −15.48 | 0.5 |
| Katona et al, 2012[43] | x | x | X | X | P | | | | −10.91 | 0.25 |
| Alvarez et al, 2012[44] | x | x | X | | P | P | | | −11.2 | 0.333 |
| Boulenger et al, 2014[12] | x | | X | | | | P | P | −11.7 | 0.25 |
| Mahableshwarkar et al, 2015[45] | x | | | | | | N | P | −12.83 | 0.25 |
| Jacobsen et al, 2015[13] | x | | X | | | N | | P | −10.77 | 0.333 |
| Mahableshwarkar et al, 2015[14] | x | | | | | N | N | | −12.87 | 0.333 |
| Nishimura et al, 2018[46] | x | | | | N | N | | N | −13.99 | 0.25 |
| Inoue et al, 2018[47] | x | x | | | N | N | | | −13.81 | 0.333 |
| Baune et al, 2018[48] | x | | | X | | P | | | −8 | 0.333 |
| McIntyre et al, 2014[49] | x | | | X | | P | | P | −10.85 | 0.333 |
| Mahableshwarkar et al, 2016[50] | x | | | X | | | | P | −12.3 | 0.333 |
| Liebowitz et al, 2017[51] | x | | X | | | | | P | −9.9 | 0.5 |
| Inoue et al, 2020[16] | x | x | | X | | P | | P | −12.37 | 0.333 |

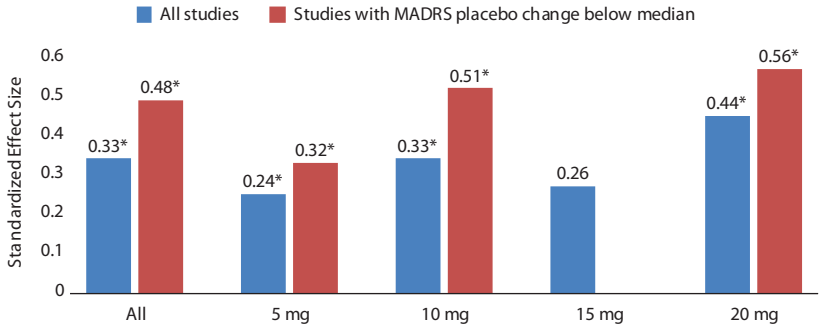
Abbreviations: DSST = Digit Substitution Test, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, N = no statistically significantly greater MADRS reduction for vortioxetine than for placebo,* P = statistically significantly greater MADRS reduction for vortioxetine than for placebo.*
*Hierarchical testing ignored.

**Table 2. Meta-Analysis Results**

| Comparison | Estimate[a] | 95% CI | *P* value | Heterogeneity *P* value | $\tau^2$ | *Q* | No. of drug-placebo comparators |
|---|---|---|---|---|---|---|---|
| Vortioxetine vs placebo | | | | | | | |
| MADRS change, all doses | 0.33 | 0.24 to 0.41 | <.0001 | <.0001 | 0.041 | NA | 29 |
| MADRS response, all doses, RR | 1.37 | 1.28 to 1.48 | <.0001 | .001 | NA | 56.185 | 29 |
| MADRS remission, all doses, RR | 1.37 | 1.25 to 1.51 | <.0001 | .025 | NA | 44.4.09 | 29 |
| HARS change, all doses | 0.26 | 0.15 to 0.37 | <.0001 | <.0001 | 0.0274 | NA | 13 |
| DSST change, all doses | 0.21 | 0.02 to 0.4 | .025 | <.0001 | 0.0489 | NA | 7 |
| Vortioxetine vs placebo MADRS change | | | | | | | |
| Vortioxetine 5 mg | 0.24 | 0.08 to 0.39 | .002 | <.0001 | 0.036 | NA | 8 |
| Vortioxetine 10 mg | 0.33 | 0.19 to 0.47 | <.0001 | .001 | 0.0335 | NA | 10 |
| Vortioxetine 15 mg | 0.26 | −0.06 to 0.58 | .118 | .005 | 0.0684 | NA | 3 |
| Vortioxetine 20 mg | 0.44 | 0.27 to 0.62 | <.0001 | <.0001 | 0.045 | NA | 8 |
| Studies with placebo change below 12.37 points | | | | | | | |
| MADRS change, all doses | 0.48 | 0.33 to 0.62 | <.0001 | <.0001 | 0.046 | NA | 12 |
| MADRS response, all doses, RR | 1.59 | 1.4 to 1.8 | <.0001 | .05 | NA | 19.703 | 12 |
| MADRS remission, all doses, RR | 1.63 | 1.43 to 1.86 | <.0001 | .44 | NA | 10.991 | 12 |
| MADRS change, vortioxetine, 5 mg only | 0.32 | 0.008 to 0.63 | .044 | .004 | 0.0625 | NA | 3 |
| MADRS change, vortioxetine, 10 mg only | 0.51 | 0.30 to 0.72 | <.0001 | .053 | 0.0277 | NA | 4 |
| MADRS change, vortioxetine, 15 mg only | NA | NA | NA | NA | NA | NA | 0 |
| MADRS change, vortioxetine, 20 mg only | 0.56 | 0.32 to 0.80 | <.0001 | .002 | 0.0531 | NA | 5 |
| HARS change, all doses | 0.28 | 0.10 to 0.45 | .002 | .001 | 0.0418 | NA | 7 |
| DSST change, all doses | 0.34 | 0.19 to 0.49 | <.0001 | .09 | 0.0146 | NA | 5 |

[a]Values are shown as SMD unless otherwise noted in the Comparison column.
Abbreviations: DSST = Digit Substitution Test, HAMA = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, RR = risk ratio, SEM = standard error of the mean, SMD = standardized mean difference.

**Figure 2. MADRS Score Change Difference for Vortioxetine Versus Placebo[a]**



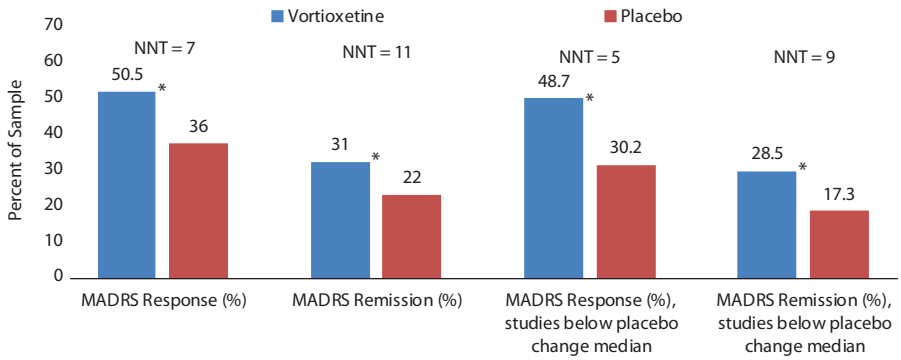

[a]Positive numbers in favor of vortioxetine:
All studies: $P < .0001$ for all doses pooled, 10 mg only, 20 mg only; $P < .01$ for 5 mg only.
Below placebo median studies: $P < .0001$ for all doses, 10 mg only, 20 mg only; $P < .05$ for 5 mg only.
*$P < .05$, random effects meta-analysis for drug vs placebo.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale

0.47), 0.26 (−0.06 to 0.58), and 0.44 (0.27 to 0.62) for 5-mg, 10-mg, 15-mg, and 20-mg doses, respectively (see Table 2). In studies that had a change in MARDS score in the placebo group that was below the median (−12.37), there was greater improvement with vortioxetine versus placebo (see Table 2 and Figure 2). Among all studies, the standardized effect size for vortioxetine over placebo was 0.26 for the HARS ($P < .0001$) and 0.21 for the DSST ($P < .05$); among studies with a change in MADRS score for placebo below the median, the corresponding effect sizes were 0.28 for the HARS ($P < .01$) and 0.34 for the DSST ($P < .0001$). Response and remission rates were higher with vortioxetine versus placebo, especially in studies in which change in MADRS score for the placebo group was below the median (see Figure 3).

## DISCUSSION

The present work is the most comprehensive published to date focusing on the efficacy of vortioxetine as monotherapy for MDD. When all randomized, double-blind, placebo-controlled trials are analyzed together, the effect size based on differences in MADRS scores (expressed as the *standardized* mean difference in change in MADRS scores over time between the two treatment groups) is, approximately, 0.33 which is equivalent to that for venlafaxine[52] and duloxetine,[53] two commonly used antidepressants. Statistically significant efficacy is also demonstrated on MADRS response rates, MADRS remission rates, anxiolytic effect as expressed by the HARS, and effect on global-executive functioning as expressed by the DSST, albeit with comparably smaller

**Figure 3. MADRS Categorical Outcomes[a]**




[a]Positive numbers in favor of vortioxetine:
All studies: $P < .0001$: MADRS response and remission vs placebo.
Below placebo median studies: $P < .0001$: MADRS response and remission vs placebo.
*$P < .05$, random effects meta-analysis for drug vs placebo.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, NNT = number needed to treat.

effect sizes than for the MADRS for the two latter measures. Important lessons, however, emerge when the efficacy of vortioxetine is examined taking into account certain key variables.

First, similar to the selective serotonin reuptake inhibitor antidepressants,[28] vortioxetine exhibits a linear starting dose–effect size relationship, with effect sizes increasing from 0.24 for the 5-mg dose to 0.33 for the 10-mg and 0.44 for the 20-mg dose. The 15-mg dose appears to be an exception to the rule. However, it is worth pointing out that only 3 drug-placebo comparisons exist for the 15-mg dose, which may account for the difference in effect size. Clearly, therefore, greater efficacy can be expected with the 20-mg starting dose than with the others. Clinicians may want to consider a more rapid titration to 20-mg daily when treating more severe cases of depression.

Second, when we examine efficacy in the overall data set as a function of degree of improvement in the placebo group, the all-too-familiar relationship emerges in which greater improvement on placebo is associated with a lower drug-versus-placebo difference in efficacy.[30,54] Examining the subset of studies with a MADRS score reduction below the median for this group of studies, the standardized effect size for vortioxetine versus placebo on the MADRS is nearly 0.5, which is quite impressive for an oral antidepressant. Similarly, the efficacy of the 20-mg starting dose for this subgroup of studies is 0.56, while that for the DSST is 0.34. In addition, the number needed to treat for response is 5 for subjects enrolled in studies below the median change in MADRS score for the placebo group. Clearly, as with most other treatments developed in the field, marginally informative or uninformative studies have masked the true effect size of this compound for MDD. Steps should be taken to minimize the risk of uninformative studies, including managing expectation bias[29,55] and ensuring proper quality assurance and independent subject vetting for eligibility.[56] Strategies that utilize careful clinical and biological assessments to identify placebo responders with high accuracy are needed[57] given that the current practice of an extensive set of eligibility criteria has restricted the generalizability of study findings.[58] These steps will reduce the probability of uninformative studies without excluding valid MDD patient populations from studies.

Several limitations should be taken into account when interpreting our findings. First, even though we have made every effort to identify any unpublished completed studies, it is impossible to be certain that such studies do not exist. These, if identified and pooled with our data, may somewhat alter the results, although to a limited degree given the size of the existing dataset. Second, the vast majority of data pertain to the use of vortioxetine for subjects between the ages of 18 and 65 years. Hence, it is difficult to try and extrapolate our findings to underrepresented subjects such as the elderly, and it is extremely speculative to try to extend these findings to subjects typically excluded from such studies including children, adolescents, pregnant or breastfeeding women, and subjects with greater severity of suicidality.[59] Finally, although half of studies pooled included the HARS, just as many did not, thus limiting the power of the meta-analysis with respect to the HARS. In addition, there was also no minimum severity requirement on this scale for subject enrollment across studies, further limiting the drug-placebo effect size. As a result, while confirming the efficacy of vortioxetine in anxious symptoms associated with MDD, our analysis is not ideally suited to better estimate the effect size of the same. Future analyses should focus on the subpopulation of patients with anxious depression as defined by Fava et al.[60]

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## REFERENCES


1. Papakostas GI, Jackson WC, Rafeyan R, et al. Inadequate response to antidepressant treatment in major depressive disorder. *J Clin Psychiatry*. 2020;81(3):OT19037COM5.
2. Papakostas GI, Jackson WC, Rafeyan R, et al. Overcoming challenges to treat inadequate response in major depressive disorder. *J Clin Psychiatry*. 2020;81(3):OT19037BR4.
3. Rafeyan R, Papakostas GI, Jackson WC, et al. Inadequate response to treatment in major depressive disorder: augmentation and adjunctive strategies. *J Clin Psychiatry*. 2020;81(3):OT19037BR3.
4. Jackson WC, Papakostas GI, Rafeyan R, et al. Recognizing inadequate response in patients with major depressive disorder. *J Clin Psychiatry*. 2020;81(3):OT19037BR2.
5. Trivedi MH, Papakostas GI, Jackson WC, et al. Implementing measurement-based care to determine and treat inadequate response. *J Clin Psychiatry*. 2020;81(3):OT19037BR1.
6. Trivedi MH. How can measurement-based care help improve treatment outcomes for major depressive disorder in primary care? *J Clin Psychiatry*. 2020;81(2):UT17042BR2C.
7. Trivedi MH. Major depressive disorder in primary care: strategies for identification. *J Clin Psychiatry*. 2020;81(2):UT17042BR1C.
8. Citrome L, Gaynes BN, Goldberg JF, et al. New mechanisms, new opportunities: integrating novel antidepressants in the treatment of major depressive disorder. *J Clin Psychiatry*. 2019;80(5):TK18061AS2C.
9. Thase ME. Current and emerging treatments to address unmet needs in MDD. *J Clin Psychiatry*. 2019;80(1):AL18009BR1C.
10. Zhang J, Mathis MV, Sellers JW, et al. The US Food and Drug Administration's perspective on the new antidepressant vortioxetine. *J Clin Psychiatry*. 2015;76(1):8–14.
11. Connolly KR, Thase ME. Vortioxetine: a new treatment for major depressive disorder. *Expert Opin Pharmacother*. 2016;17(3):421–431.
12. Boulenger JP, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol*. 2014;29(3):138–149.
13. Jacobsen PL, Mahableshwarkar AR, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of vortioxetine 10 mg and 20 mg in adults with major depressive disorder. *J Clin Psychiatry*. 2015;76(5):575–582.
14. Mahableshwarkar AR, Jacobsen PL, Serenko M, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of 2 doses of vortioxetine in adults with major depressive disorder. *J Clin Psychiatry*. 2015;76(5):583–591.
15. Baune BT, Brignone M, Larsen KG. A network meta-analysis comparing effects of various antidepressant classes on the Digit Symbol Substitution Test (DSST) as a measure of cognitive dysfunction in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2018;21(2):97–107.
16. Inoue T, Sasai K, Kitagawa T, et al. Randomized, double-blind, placebo-controlled study to assess the efficacy and safety of vortioxetine in Japanese patients with major depressive disorder. *Psychiatry Clin Neurosci*. 2020;74(2):140–148.
17. Papakostas GI. Antidepressants and their effect on cognition in major depressive disorder. *J Clin Psychiatry*. 2015;76(8):e1046.
18. Papakostas GI, Culpepper L. Understanding and managing cognition in the depressed patient. *J Clin Psychiatry*. 2015;76(4):418–425.
19. Berhan A, Barker A. Vortioxetine in the treatment of adult patients with major depressive disorder: a meta-analysis of randomized double-blind controlled trials. *BMC Psychiatry*. 2014;14(1):276.
20. Meeker AS, Herink MC, Haxby DG, et al. The safety and efficacy of vortioxetine for acute treatment of major depressive disorder: a systematic review and meta-analysis. *Syst Rev*. 2015;4(1):21.
21. Pae CU, Wang SM, Han C, et al. Vortioxetine: a meta-analysis of 12 short-term, randomized, placebo-controlled clinical trials for the treatment of major depressive disorder. *J Psychiatry Neurosci*. 2015;40(3):174–186.
22. Baldwin DS, Florea I, Jacobsen PL, et al. A meta-analysis of the efficacy of vortioxetine in patients with major depressive disorder (MDD) and high levels of anxiety symptoms. *J Affect Disord*. 2016;206:140–150.
23. Thase ME, Mahableshwarkar AR, Dragheim M, et al. A meta-analysis of randomized, placebo-controlled trials of vortioxetine for the treatment of major depressive disorder in adults. *Eur Neuropsychopharmacol*. 2016;26(6):979–993.
24. Koesters M, Ostuzzi G, Guaiana G, et al. Vortioxetine for depression in adults. *Cochrane Database Syst Rev*. 2017;7(7):CD011520.
25. Nomikos GG, Tomori D, Zhong W, et al. Efficacy, safety, and tolerability of vortioxetine for the treatment of major depressive disorder in patients aged 55 years or older. *CNS Spectr*. 2017;22(4):348–362.
26. Christensen MC, Florea I, Lindsten A, et al. Efficacy of vortioxetine on the physical symptoms of major depressive disorder. *J Psychopharmacol*. 2018;32(10):1086–1097.
27. Zheng J, Wang Z, Li E. The efficacy and safety of 10 mg/day vortioxetine compared to placebo for adult major depressive disorder: a meta-analysis. *Afr Health Sci*. 2019;19(1):1716–1726.
28. Papakostas GI, Charles D, Fava M. Are typical starting doses of the selective serotonin reuptake inhibitors sub-optimal? a meta-analysis of randomized, double-blind, placebo-controlled, dose-finding studies in major depressive disorder. *World J Biol Psychiatry*. 2010;11(2 pt 2):300–307.
29. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009;19(1):34–40.
30. Iovieno N, Nierenberg AA, Parkin SR, et al. Relationship between placebo response rate and clinical trial outcome in bipolar

depression. *J Psychiatr Res*. 2016;74:38–44.
31. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
32. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
33. Jaeger J. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol*. 2018;38(5):513–519.
34. Lenze EJ, Stevens A, Waring JD, et al. Augmenting computerized cognitive training with vortioxetine for age-related cognitive decline: a randomized controlled trial. *Am J Psychiatry*. 2020;177(6):548–555.
35. Vieta E, Florea I, Schmidt SN, et al. Intravenous vortioxetine to accelerate onset of effect in major depressive disorder: a 2-week, randomized, double-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2019;34(4):153–160.
36. Nierenberg AA, Loft H, Olsen CK. Treatment effects on residual cognitive symptoms among partially or fully remitted patients with major depressive disorder: a randomized, double-blinded, exploratory study with vortioxetine. *J Affect Disord*. 2019;250:35–42.
37. Smith J, Browning M, Conen S, et al. Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. *Mol Psychiatry*. 2018;23(5):1127–1133.
38. Boulenger JP, Loft H, Florea I. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. *J Psychopharmacol*. 2012;26(11):1408–1416.
39. Baldwin DS, Loft H, Dragheim M. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). *Eur Neuropsychopharmacol*. 2012;22(7):482–491.
40. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. *Curr Med Res Opin*. 2013;29(3):217–226.
41. Jain R, Mahableshwarkar AR, Jacobsen PL, et al. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol*. 2013;16(2):313–321.
42. Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*. 2012;73(7):953–959.
43. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*. 2012;27(4):215–223.
44. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2012;15(5):589–600.
45. Mahableshwarkar AR, Jacobsen PL, Chen Y, et al. A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD. *Psychopharmacology (Berl)*. 2015;232(12):2061–2070.
46. Nishimura A, Aritomi Y, Sasai K, et al. Randomized, double-blind, placebo-controlled 8-week trial of the efficacy, safety, and tolerability of 5, 10, and 20 mg/day vortioxetine in adults with major depressive disorder. *Psychiatry Clin Neurosci*. 2018;72(2):64–72.
47. Inoue T, Nishimura A, Sasai K, et al. Randomized, 8-week, double-blind, placebo-controlled trial of vortioxetine in Japanese adults with major depressive disorder, followed by a 52-week open-label extension trial. *Psychiatry Clin Neurosci*. 2018;72(2):103–115.
48. Baune BT, Sluth LB, Olsen CK. The effects of vortioxetine on cognitive performance in working patients with major depressive disorder: a short-term, randomized, double-blind, exploratory study. *J Affect Disord*. 2018;229:421–428.
49. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014;17(10):1557–1567.
50. Mahableshwarkar AR, Zajecka J, Jacobson W, et al. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. *Neuropsychopharmacology*. 2016;41(12):2961.
51. Liebowitz MR, Careri J, Blatt K, et al. Vortioxetine versus placebo in major depressive disorder comorbid with social anxiety disorder. *Depress Anxiety*. 2017;34(12):1164–1172.
52. Thase M, Asami Y, Wajsbrot D, et al. A meta-analysis of the efficacy of venlafaxine extended release 75–225 mg/day for the treatment of major depressive disorder. *Curr Med Res Opin*. 2017;33(2):317–326.
53. Ball SG, Desaiah D, Zhang Q, et al. Efficacy and safety of duloxetine 60 mg once daily in major depressive disorder: a review with expert commentary. *Drugs Context*. 2013;2013:212245.
54. Gopalakrishnan M, Zhu H, Farchione TR, et al. The trend of increasing placebo response and decreasing treatment effect in schizophrenia trials continues: an update from the US Food and Drug Administration. *J Clin Psychiatry*. 2020;81(2):19r12960.
55. Salloum NC, Fava M, Ball S, et al. Success and efficiency of phase 2/3 adjunctive trials for MDD funded by industry: a systematic review. *Mol Psychiatry*. 2020;25(9):1967–1974.
56. Papakostas GI, Østergaard SD, Iovieno N. The nature of placebo response in clinical studies of major depressive disorder. *J Clin Psychiatry*. 2015;76(4):456–466.
57. Trivedi MH, South C, Jha MK, et al. A novel strategy to identify placebo responders: prediction index of clinical and biological markers in the EMBARC Trial. *Psychother Psychosom*. 2018;87(5):285–295.
58. Zimmerman M, Balling C, Chelminski I, et al. Have treatment studies of depression become even less generalizable? applying the inclusion and exclusion criteria in placebo-controlled antidepressant efficacy trials published over 20 years to a clinical sample. *Psychother Psychosom*. 2019;88(3):165–170.
59. Iltis AS, McCall WV, Deria R. Suicidality, depression, and the FDA: health inequities and the ethical conduct of research. *J Clin Psychiatry*. 2020;81(2):19m13050.
60. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry*. 2008;165(3):342–351.