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Review

# Balancing benefits and harms of treatments for acute bipolar depression

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ABSTRACT

*Background:* Bipolar depression is more pervasive than mania, but has fewer evidence-based treatments.
*Methods:* Using data from multicenter, randomized, double-blind, placebo-controlled trials and meta-analyses, we assessed the number needed to treat (NNT) for response and the number needed to harm (NNH) for selected side effects for older and newer acute bipolar depression treatments.
*Results:* The 2 older FDA-approved treatments for bipolar depression, olanzapine-fluoxetine combination (OFC) and quetiapine (QTP) monotherapy, were efficacious (response NNT=4 for OFC, NNT=6 for QTP), but similarly likely to yield harms (OFC weight gain NNH=6; QTP sedation/somnolence NNH=5). Commonly used unapproved agents (lamotrigine monotherapy and adjunctive antidepressants) tended to be well-tolerated (with double-digit NNHs), although this advantage was at the cost of inadequate efficacy (response NNT=12 for lamotrigine, NNT=29 for antidepressants). In contrast, the newly approved agent lurasidone was not only efficacious (response NNT=5 for monotherapy, NNT=7 as adjunctive therapy), but also had enhanced tolerability (NNH=15 for akathisia [monotherapy], NNH=16 for nausea [adjunctive]). Although adjunctive armodafinil appeared well tolerated, its efficacy in bipolar depression has not been consistently demonstrated in randomized controlled trials.
*Limitations:* NNT and NNH are categorical metrics; only selected NNHs were assessed; limited generalizability of efficacy (versus effectiveness) studies.
*Conclusions:* For acute bipolar depression, older approved treatments may have utility in high-urgency situations, whereas lamotrigine and antidepressants may have utility in low-urgency situations. Newly approved lurasidone may ultimately prove useful in diverse situations. New drug development needs to focus on not only efficacy but also on tolerability.



**Contents**



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## 1. Introduction

Bipolar disorder (BD) is a common, recurrent, frequently debilitating and, in many instances, tragically fatal illness, characterized by oscillations in mood, energy, and ability to function (American Psychiatric Association, 2013). BD, in its broadest sense, may affect as much as 4% of the population (Merikangas et al., 2007) and ranks second among mental illnesses causing disability in working-age adults (Murray and Lopez, 1997). Depressive compared with manic states are more pervasive (Judd et al., 2003; Judd et al., 2002) and, thus, crucially contribute to functional impairment (Altshuler et al., 2002; Judd et al., 2005). Although approximately 20% of BD patients may attempt suicide (Rihmer and Kiss, 2002), most often during depression (Pompili et al., 2013; Valtonen et al., 2008), many succumb to premature cardiovascular, cerebrovascular, gastrointestinal, or other medical causes of mortality (Osby et al., 2001). There are fewer evidence-based treatments for bipolar depression than for mania, and the older treatments approved by the US Food and Drug Administration (FDA) for acute bipolar depression involve risks of substantial side effects, such as sedation/somnolence that can impair function and weight gain/metabolic complications that can increase the risk of mortality (Sanford and Keating, 2012; Silva et al., 2013). This suggests that new, well-tolerated, effective treatment options are needed. In this article, we describe an approach for evaluating the potential benefits and risks of older, newer approved, unapproved, and emerging treatments for acute bipolar depression.

## 2. Methods

### *2.1 Data sources*

The published scientific literature and proceedings of recent major scientific meetings (e.g., the American Psychiatric Association, the American College of Neuropsychopharmacology) were searched for randomized, double-blind, placebo-controlled trials of the efficacy of pharmacotherapies for acute bipolar depression. For the published scientific literature, the PubMed database was searched using the search terms "bipolar," "bipolar disorder," "bipolar I disorder," "bipolar II disorder," "bipolar depression," "randomized," "controlled," "treatment," "efficacy," "effectiveness," "lithium," "carbamazepine," "divalproex," "valproate," "lamotrigine," "olanzapine," "risperidone," "quetiapine," "ziprasidone," "aripiprazole," "asenapine," "lurasidone," "antidepressants," and "armodafinil".

### *2.2 Study selection*

Large ($N$>100), randomized, double-blind, placebo-controlled trials of the efficacy of pharmacotherapies for acute bipolar depressive episodes in patients with well-defined bipolar I disorder or bipolar II disorder were selected. For antidepressants, a recent meta-analysis was selected. Studies whose primary emphasis was not the treatment of BD and studies not reporting response/remission rates and side effect rates were excluded.

### *2.3 Outcome measures*

The efficacy variable was number needed to treat (NNT) for acute response (percentage of subjects with at least 50% improvement in mood rating) compared with placebo for acute bipolar depressive episodes. NNT, the expected number of subjects who would need to be treated to yield 1 additional good outcome, compared with a control intervention (Citrome, 2008; Citrome, 2009b; Laupacis et al., 1988), was calculated for response in acute bipolar depression (i.e., at least a 50% decrease in depressive symptoms), by assessing the reciprocal of the absolute risk reduction (difference in the response rates for a treatment and a control intervention) (Citrome, 2008; Laupacis et al., 1988). For example, if a medication and placebo had response rates of 50% and 25%, respectively, the NNT for response was 100% / (50%–25%) = 100% / 25% = 4. That is, 4 patients would need to be treated to expect to obtain 1 more response compared with placebo. We followed the convention of rounding up NNT to the next higher integer (Sackett and Straus, 1998), although some have advocated that NNTs from 1 to 100 ought to be reported to at least 1 decimal place (Stang et al., 2010). Lower NNTs represented better outcomes, with single digits (preferably low single digits) generally representing adequate outcomes in BD.

Harms (adverse effects) were quantified using the number needed to harm (NNH), the number of patients who would have to be treated before 1 additional patient would be expected to experience an adverse effect, compared with a control intervention (Ketter et al., 2011). NNH for adverse effects were calculated by assessing the reciprocal of the absolute risk increase (difference in the adverse effect rates for a treatment and a control intervention). For example, if a medication and placebo had sedation/somnolence rates of 40% and 20%, respectively, the NNH for sedation/somnolence was 100% / (40% – 20%) = 100% / 20% = 5. That is, 5 patients would need to be treated to expect to encounter 1 more with sedation/somnolence compared with placebo. We followed the convention of rounding up NNH to the next higher integer.

Ninety-five percent confidence intervals (95% CIs) for NNT and NNH were also calculated to facilitate comparisons of likelihoods of benefits (NNTs) versus harms (NNHs) (Citrome, 2009a). In instances where there was no significant difference between active treatment and placebo with respect to efficacy (NNT) and/or tolerability (NNH), the (infinite/discontinuous) 95% CI was reported as not significant (NS). In other instances (with finite, continuous 95% CIs for both NNT and NNH), if the upper limit of the 95% CI for NNT was less than the lower limit of the 95% CI for NNH, the active treatment was deemed more likely to yield benefit than harm; if the 95% CIs for NNT and NNH overlapped, the active treatment was deemed comparably likely to yield benefit and harm; and if the upper limit of the 95% CI for NNH was less than the lower limit of the 95% CI for NNT, the active treatment was deemed to be more likely to yield harm than benefit.

For each bipolar depression medication we determined the clinically relevant adverse effect resulting in the greatest increase in harm over placebo (i.e., the adverse effect yielding the lowest NNH, based on available published data). Thus, we reported NNH

**Table 1**
FDA-approved treatments for bipolar disorder.*

| Acute Mania | | Acute Bipolar Depression | | Bipolar Maintenance | |
|---|---|---|---|---|---|
| Year† | Drug | Year† | Drug | Year† | Drug |
| 1970 | Lithium (P) | 2003 | Olanzapine + fluoxetine combination | 1974 | Lithium (P) |
| 1973 | Chlorpromazine | 2006 | Quetiapine, XR (2008) | 2003 | Lamotrigine |
| 1994 | Divalproex, ER (2005) | 2013 | Lurasidone‡ | 2004 | Olanzapine |
| 2000 | Olanzapine (P)‡ | | | 2005 | Aripiprazole (P)‡ |
| 2003 | Risperidone (P)‡ | | | 2008 | Quetiapine, XR (adjunct) |
| 2004 | Quetiapine, XR (2008) (P)‡ | | | 2009 | Risperidone LAI‡ |
| 2004 | Ziprasidone | | | 2009 | Ziprasidone (adjunct) |
| 2004 | Aripiprazole (P)‡ | | | | |
| 2004 | Carbamazepine ERC | | | | |
| 2009 | Asenapine‡ | | | | |

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† Year indicates when FDA adult approval was granted for these indications.
‡ Adjunctive and monotherapy.
ER, ERC, XR = extended-release oral formulations, FDA = US Food and Drug Administration, LAI = long-acting injectable formulation, P = pediatric and adult.

for sedation/somnolence for quetiapine and lamotrigine, at least 7% weight gain for olanzapine and olanzapine plus fluoxetine, treatment-emergent affective switch (TEAS) for antidepressants as a class and paroxetine specifically, akathisia/nausea for lurasidone monotherapy/adjunctive therapy, and anxiety for armodafinil adjunctive therapy.

### *2.4 Data extraction*

Two of the authors (S.M. and T.K.) extracted data from individual studies. The following data were recorded: authors and years of publication, number of subjects using active treatments and control interventions, doses, NNT, NNH, and related 95% CIs.

### *2.5 Data analysis*

Analyses of NNT for response and NNH for side effects, and related 95% CIs were conducted using the retrieved reports. When more than one study was available for a particular agent, overall NNT, NNH, and related 95% CIs were obtained by sample-size weighted pooling of individual study data.

## 3. Currently available treatments

As of late 2014, the FDA had approved pharmacotherapy indications for 13 treatments for the management of BD (Table 1) (Ketter and Wang, 2010). These indications were based on treatment phases. Most of the approved indications were for acute mania, including 10 monotherapy approvals and 5 adjunctive therapies (added to lithium or valproate). In contrast, for the indication of acute bipolar depression, only 2 monotherapies (lurasidone, quetiapine), 1 combination therapy (olanzapine plus fluoxetine), and 1 adjunctive therapy (lurasidone, added to lithium or valproate) had been approved. Only 1 agent (quetiapine) had FDA indications for both acute mania and acute bipolar depression.

Although the mood stabilizers (MSs) lithium, valproate, lamotrigine, and carbamazepine are opined by some to be the foundational pharmacotherapies for BD, second-generation antipsychotics (SGAs) have been increasingly used (Ketter et al., 2011). In addition, antidepressants, other anticonvulsants, and novel therapeutic agents are commonly combined with MSs and SGAs in clinical settings (Ketter et al., 2011).

Evidence-based treatment of BD generally begins with considering agents approved by the FDA, because such interventions are considered the most well-established management options, having demonstrated efficacy and safety/tolerability in adequately sized, multicenter, randomized, double-blind, placebo-controlled trials (Table 1). However, clinical needs commonly exceed the management options supported by FDA indications. In such instances, the next-best treatments are those supported by at least 1 adequately sized, randomized, double-blind, placebo-controlled trial. For bipolar depression, the need for treatments with adequate tolerability has been so significant that interventions with adequate tolerability but inadequate evidence of efficacy, such as lamotrigine and adjunctive antidepressants, have been commonly used in the absence of options with both adequate efficacy and tolerability.

## 4. Assessment of potential benefits versus harms

The potential benefits (therapeutic effects) of treatments for BD must be considered in the context of potential harms (adverse effects). Although the existence of potential benefits and the possibility of being worthwhile, in spite of risks of potential harms, can be imputed via the existence of FDA indications, clinicians and patients commonly desire more detailed assessments of benefit versus harm.

In recent years, studies have increasingly quantified potential benefits and harms by analyzing NNT and NNH, respectively, which were described in detail earlier, in section 2.3. Most FDA-approved treatments for BD have single-digit NNTs (Ketter et al., 2011). Alternative treatments worth considering may have NNTs as high as the low teens in the setting of good tolerability and few well-tolerated agents with lower NNTs.

All of the approved treatments for BD have at least 1 boxed warning regarding the risk of serious adverse effects (Ketter et al., 2011). Although such boxed warnings are clearly important, they do not generally represent the most common adverse effects that cause treatment discontinuation (e.g., sedation/somnolence, weight gain, and akathisia) (Ketter et al., 2011). Higher NNHs represent better outcomes, with double digits generally representing adequate outcomes, depending on the severity of the harm (Ketter et al., 2011). Because treatments should be more likely to help than to harm, we strive for interventions with lower NNTs than NNHs, commonly with a goal of having no more than a single-digit NNT (i.e., at least 10% more efficacy than placebo) and at least a double-digit NNH (i.e., no more than 10% excess risk of adverse effects over placebo) (Ketter et al., 2011). Striving for an NNH higher than twice the NNT can further increase the likelihood of good versus bad outcomes, with help being more than twice as likely as harm compared with placebo.

In this article, for each acute bipolar depression medication we report NNH for the clinically relevant adverse effect resulting in

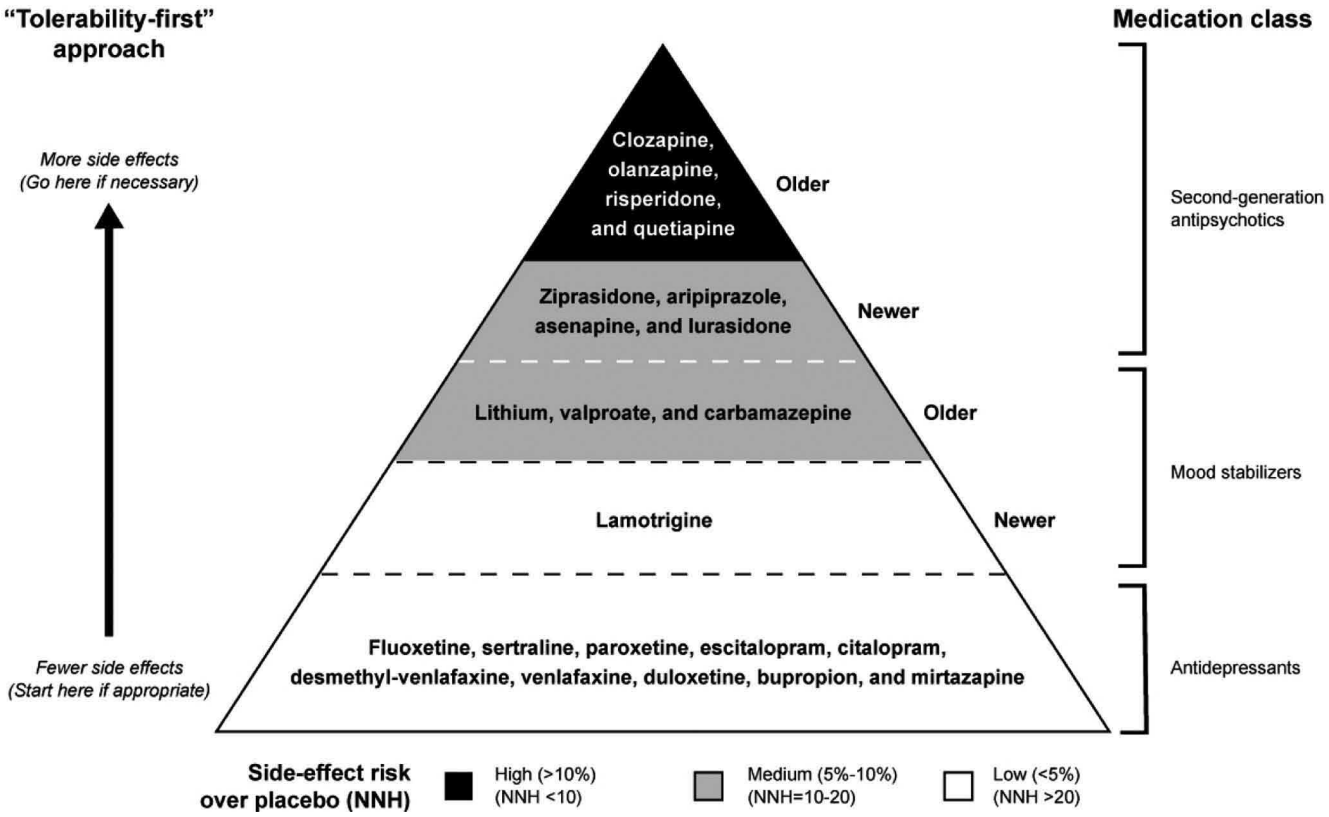


**Fig 1.** Schematic for adverse effects of psychotropic medications. The rank orders for potency may be perceived to be broadly similar for the therapeutic and adverse effects of psychotropic medications, ranging from highest to lowest as follows: (1) second-generation antipsychotics (SGAs), (2) mood stabilizers (MSs; other than lamotrigine), and (3) lamotrigine/antidepressants, although systematic data supporting this notion are limited. However, newer compared with older treatment options commonly represent tolerability enhancements. Hence, the newer SGAs ziprasidone, aripiprazole, asenapine, and lurasidone may entail less risk of adverse effects than the older SGAs clozapine, olanzapine, risperidone, and quetiapine. Similarly, the newer MS lamotrigine may entail less risk of adverse effects than the older MSs lithium, valproate, and carbamazepine. The antidepressants fluoxetine, sertraline, paroxetine, escitalopram, citalopram, desmethyl-venlafaxine, venlafaxine, duloxetine, bupropion, and mirtazapine may entail fewer adverse effect risks than the MSs or SGAs. Clinicians commonly adopt a "tolerability-first" approach, starting (if appropriate) with agents with fewer side effects at the potential expense of poorer efficacy before moving on (if necessary) to agents with more robust efficacy at the potential expense of poorer tolerability. NNH = number needed to harm.

the greatest increase in harm over placebo (i.e,. the adverse effect yielding the lowest NNH, based on available published data). For example, although many clinicians are concerned about the potential for serious rash as an adverse effect of lamotrigine, the prevalence of serious rash in lamotrigine-treated patients is low (1 in 1000 to 1 in 2000) (Calabrese et al., 2002), and placebo-controlled studies of lamotrigine for acute bipolar depression yielded an NNH for benign rash of 44 (Calabrese et al., 2008; Ketter et al., 2011). However, the NNH for sedation/somnolence in such studies was 37 (Calabrese et al., 2008). We therefore report NNH for sedation/somnolence as the most clinically relevant harm to consider when evaluating potential risks and benefits of lamotrigine treatment for acute bipolar depression. Alternative measures of potential harms that we do not report in this article include NNH for all-cause discontinuation and NNH for adverse-effect–related discontinuation of drug compared with placebo. Although such metrics may yield more integrative information about medication tolerability than NNHs for individual adverse effects, discontinuation rates in clinical trials may be confounded by variable degrees of patient motivation to complete the study. As a result, NNHs for all-cause and adverse-effect–related discontinuation may underestimate clinically relevant harms associated with a drug compared with placebo that are likely to be encountered in routine practice. Indeed, such NNHs are commonly higher than those for spontaneously reported specific adverse effects, and occasionally are even negative.

Risk-management strategies vary markedly among clinicians as well as among patients, so it is crucial to personalize benefit-versus-harm assessments. It is commonly opined that treatments that are more potent with respect to therapeutic effects (i.e., have lower NNTs) also tend to be more potent with respect to adverse effects (i.e., have lower NNHs), whereas treatments that are more tolerable (i.e., have lower risk of adverse effects and higher NNHs) also tend to be less potent with respect to therapeutic effects (i.e., have higher NNTs). However, systematic data supporting such opinions are limited. Some investigators believe that the rank orders for potency for both therapeutic and adverse effects of interventions may be broadly similar within drug classes, and by class from highest to lowest may be: (1) SGAs, (2) MSs (other than lamotrigine), and (3) lamotrigine and antidepressants (Figure 1). Again, however, systematic data supporting this notion are limited.

In the clinical management of more urgent situations (e.g., treatment of severe acute symptoms), a compelling and immediate need for efficacy (i.e., lower NNT) may mitigate the increased risk of adverse effects (i.e., lower NNH) of more potent treatments, such as SGAs (Ketter et al., 2011). During less urgent situations (e.g., treatment of mild subacute symptoms or during maintenance treatment), a greater need for tolerability (i.e., higher NNH) may mitigate the increased risk of inefficacy (i.e., higher NNT) of more tolerable treatments (Ketter et al., 2011). In fact, it is common to encounter the clinical approach of starting, in less urgent situations, with better-tolerated treatments (such as lamotrigine or antidepressants, if appropriate) in spite of less robust therapeutic effects, before proceeding to treatments with greater potential therapeutic effects (such as MSs and SGAs, if necessary) but also potentially greater risks of adverse effects.

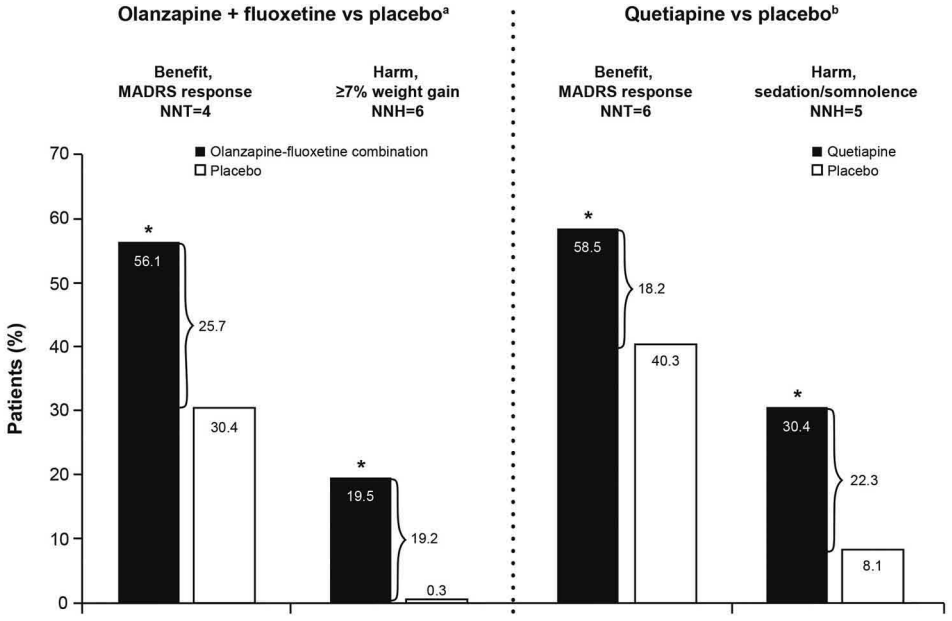


**Fig 2.** Benefits and harms of older approved bipolar depression treatments: olanzapine-fluoxetine combination (OFC) and quetiapine. Number needed to treat (response) and number needed to harm (adverse effect rates). Older approved treatments were similarly likely to yield benefit and harm compared with placebo. [a]Data from Tohen et al, 2003, Arch. Gen. Psychiatry, 60 (11), 1079–1088. Number of patients, OFC vs. placebo: *N*=82 OFC, *N*=335 placebo. [b]Data from Calabrese et al, 2005, Am. J. Psychiatry, 162 (7), 1351–1360; Thase et al, 2006, J. Clin. Psychopharmacol, 26 (6), 600–609. Number of patients, quetiapine vs. placebo: *N*=648 quetiapine benefit, *N*=330 placebo benefit, *N*=698 quetiapine harm, *N*=347 placebo harm. *$p<0.001$ vs. placebo. Adapted with permission from the Handbook of Diagnosis and Treatment of Bipolar Disorders, (Copyright © 2010). American Psychiatric Association. (Wang and Ketter, 2010). All rights reserved. MADRS = Montgomery–Åsberg Depression Rating Scale, NNH = number needed to harm, NNT = number needed to treat.

Controlled trials (at least for acute mania) support the notion that combination therapy has more potency than monotherapy for both therapeutic and adverse effects (Scherk et al., 2007; Smith et al., 2007). Thus, a common approach in less urgent situations is to start with monotherapy (if appropriate) before proceeding to combination therapy (if necessary).

## 5. Treatments for bipolar depression

In 2003, the first treatment for acute bipolar depression – olanzapine plus fluoxetine combination – received FDA approval for patients with bipolar I disorder (Tohen et al., 2003). In 2006, quetiapine monotherapy received FDA approval for acute bipolar depression, not only in patients with bipolar I disorder, but also in patients with bipolar II disorder (Calabrese et al., 2005; Thase et al., 2006). Unfortunately, subsequent adequately sized, multicenter, randomized, double-blind, placebo-controlled trials of aripiprazole (as monotherapy [Thase et al., 2008]) and ziprasidone (as monotherapy [Lombardo et al., 2012] and as an adjunct to lithium, valproate, or lamotrigine [Sachs et al., 2011]) for acute bipolar depression were negative. However, as described in detail below, in 2013, the SGA lurasidone received FDA approval for acute bipolar depression in patients with bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate.

For the two older FDA-approved treatments for acute bipolar depression, double-blind, placebo-controlled studies yielded similar single-digit (i.e., <10) NNTs for response compared with placebo (4 [95% CI 3–8] for the olanzapine plus fluoxetine combination and 6 [5–9] for quetiapine monotherapy) (Figure 2) (Calabrese et al., 2005; Thase et al., 2006; Tohen et al., 2003; Wang and Ketter, 2010). However, these treatments also had single-digit NNHs (6 [4–10] for at least 7% weight gain with the olanzapine plus fluoxetine combination, and 5 [4–5] for sedation/somnolence with quetiapine). Thus, although these two older FDA-approved treatments had adequate efficacy, their utility was substantially limited by being comparably likely to yield benefits (response) and harms (side effects) compared with placebo.

For olanzapine monotherapy, 2 double-blind, placebo-controlled studies yielded similar double-digit NNTs for response compared with placebo (12 [7–63] in the first study and 11 [6–1130] in the second study) (Figure 3) (Tohen et al., 2012; Tohen et al., 2003; Wang and Ketter, 2010). Moreover, these treatments had single-digit NNHs for at least 7% weight gain (6 [5–7] in the first study and 5 [4–6] in the second study). Thus, although olanzapine monotherapy had evidence of limited efficacy, its utility was even more substantially limited by almost (the 95% CIs of the single-digit NNHs barely overlapped those of the double-digit NNTs) being more likely to yield harm (7% weight gain) than benefit (response) compared with placebo.

Given that only 3 treatments for acute bipolar depression are FDA approved, and the 2 older such treatments are similarly likely to yield side effects and response, clinicians have commonly considered the use of other treatment options with better tolerability, even though these other treatments lack FDA approval for acute bipolar depression.

Lamotrigine is FDA-approved for bipolar I maintenance treatment, with a particular ability to delay depressive as opposed to manic episodes. Aside from serious rash, which may occur in as many as 1 in 1000 patients with BD (GlaxoSmithKline, 2011), lamotrigine has a tolerability profile similar to that of antidepressants and superior to that of SGAs and other MSs, such as lithium, divalproex, or carbamazepine (Figure 1). In double-blind, placebo-controlled studies of acute bipolar depression, lamotrigine had a favorable double-digit NNH for sedation/somnolence of 37 (95% CI was NS); however, this was in the context of an unfavorable double-digit NNT for response of 12 (8–41) (Figure 4, left) (Calabrese et al., 2008; Geddes et al., 2009; Wang and Ketter, 2010). Thus, although for lamotrigine NNH was more than three times the NNT, the favorable benefit/harm ratio was offset by inadequate efficacy (as indicated by a double-digit NNT).

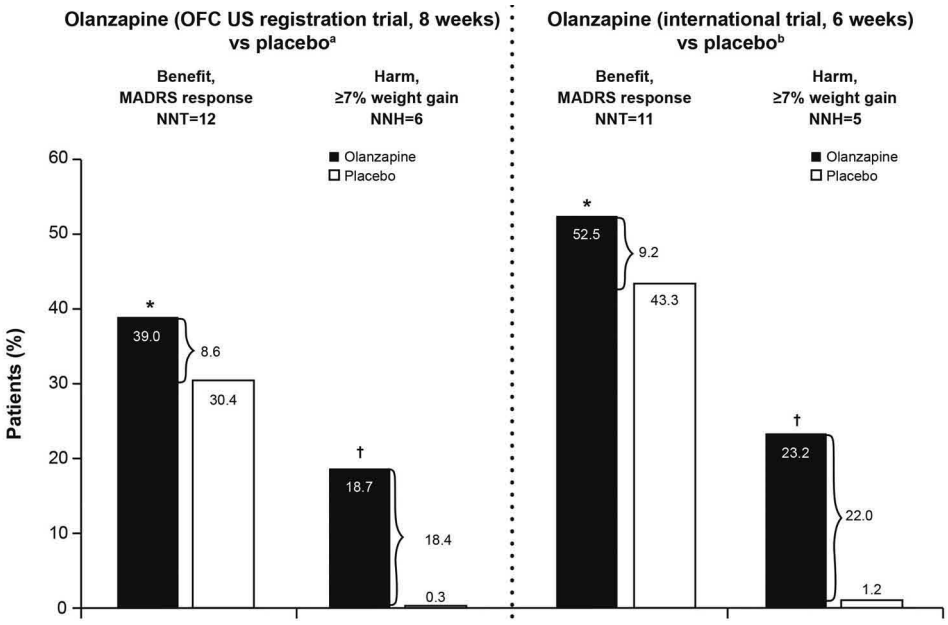


**Fig 3.** Benefits and harms of unapproved bipolar depression treatment: olanzapine. Number needed to treat (response) and number needed to harm (adverse effect rates). Olanzapine was almost more likely to yield harm as benefit compared with placebo, with inadequate efficacy. [a]Data from Tohen et al, 2003, Arch. Gen. Psychiatry, 60 (11), 1079–1088; Number of patients, OFC US trial: *N*=351 olanzapine benefit, *N*=355 placebo benefit, *N*=347 olanzapine harm, *N*=355 placebo harm. [b]Data from Tohen et al, 2012, Br. J. Psychiatry, 201 (5), 376–382; Number of patients, International trial: *N*=343 olanzapine benefit, *N*=171 placebo benefit, *N*=341 olanzapine harm, *N*=169 placebo harm. *$p<0.05$ vs. placebo. †$p<0.001$ vs. placebo. Adapted with permission from the Handbook of Diagnosis and Treatment of Bipolar Disorders, (Copyright © 2010). American Psychiatric Association. (Wang and Ketter, 2010). All rights reserved. MADRS = Montgomery–Åsberg Depression Rating Scale, NNH = number needed to harm, NNT = number needed to treat, OFC = olanzapine-fluoxetine combination.

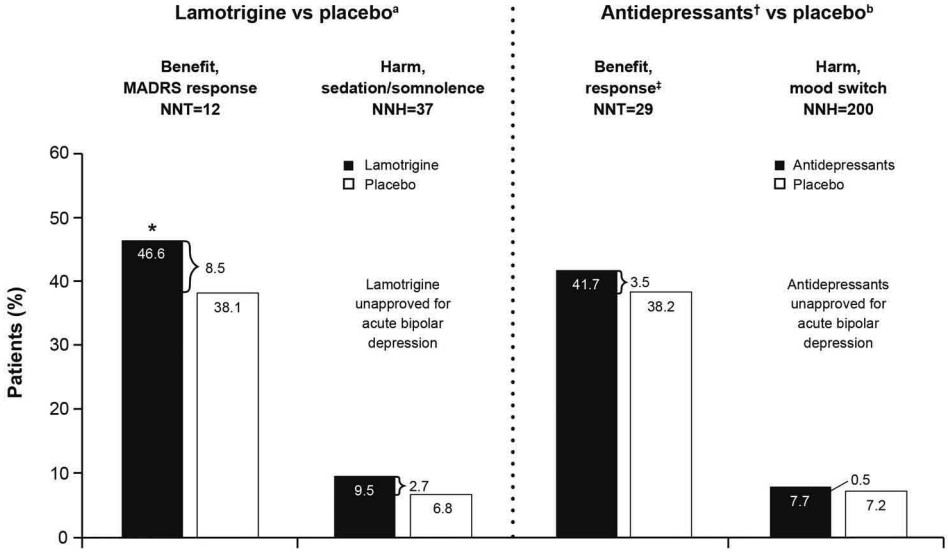


**Fig 4.** Benefits and harms of older unapproved bipolar depression treatments: lamotrigine and antidepressants. Number needed to treat (response/remission) and number needed to harm (adverse effect rates). Lamotrigine and antidepressants were unlikely to yield harm compared with placebo, but at the cost of inadequate efficacy. [a]Data from Calabrese et al, 2008, Bipolar Disord., 10 (2), 323–333; Geddes et al, 2009, Br. J. Psychiatry, 194 (1), 4–9; Number of patients, lamotrigine vs. placebo: *N*=541 lamotrigine benefit, *N*=530 placebo benefit, *N*=402 lamotrigine harm, *N*=397 placebo harm. [b]Data from Sidor and MacQueen, 2011, J. Clin. Psychiatry, 72 (2), 156–167; Number of patients, antidepressants vs. placebo: *N*=410 antidepressants benefit, *N*=608 placebo benefit, *N*=416 antidepressants harm, *N*=610 placebo harm. *$p<0.01$ vs. placebo. †Antidepressants used in the studies included in the meta-analysis were paroxetine, fluoxetine, imipramine, and bupropion. ‡One antidepressant study in this analysis assessed remission instead of response. Adapted with permission from the Handbook of Diagnosis and Treatment of Bipolar Disorders, (Copyright © 2010). American Psychiatric Association. (Wang and Ketter, 2010). All rights reserved. MADRS = Montgomery–Åsberg Depression Rating Scale, NNH = number needed to harm, NNT = number needed to treat.

Although antidepressants are very commonly administered for acute bipolar depression (Baldessarini et al., 2007), they generally (aside from fluoxetine combined with olanzapine) lack multicenter, randomized controlled trials demonstrating efficacy for bipolar depression or FDA indications for bipolar depression. The reasons underlying the common use of antidepressants in bipolar depression are likely complex, but may include their adequate efficacy in unipolar major depressive disorder; their adequate somatic tolerability, which is superior to that of MSs and SGAs (Figure 1); and the limited number of FDA-approved treatments for acute bipolar depression (Baldessarini et al., 2007). However, substantial concerns have been raised that antidepressants in BD patients may be ineffective (Nemeroff et al., 2001; Sachs et al., 2007) or may yield TEAS (Truman et al., 2007).

A recent meta-analysis of 6 double-blind, placebo-controlled studies of primarily adjunctive (added to antimanic agents)

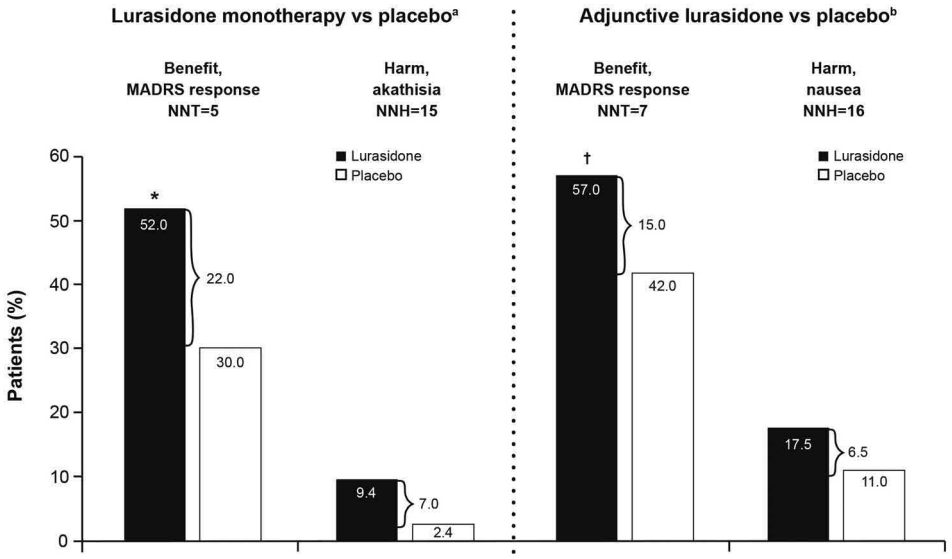


**Fig 5.** Benefits and harms of newer approved bipolar depression treatment: lurasidone. Number needed to treat (response) and number needed to harm (adverse effect rates). Lurasidone monotherapy was more likely to yield benefit than harm, compared with placebo, with adequate efficacy. Lurasidone adjunctive therapy was numerically more likely to yield benefit than harm compared with placebo. The mean modal daily dose of lurasidone, low- and high-dose groups combined, was 62.7 mg/day in the monotherapy study and 66.3 mg/day in the adjunctive study. [a]Data from Loebel et al, 2014a, Am. J. Psychiatry, 171 (2), 160–168; Number of patients, lurasidone monotherapy vs. placebo: *N*=323 lurasidone benefit, *N*=162 placebo benefit, *N*=331 lurasidone harm, *N*=168 placebo harm. [b]Data from Loebel et al, 2014b, Am. J. Psychiatry, 171 (2), 169–177; Number of patients, adjunctive lurasidone vs. placebo: *N*=179 lurasidone benefit, *N*=161 placebo benefit, *N*=183 lurasidone harm, *N*=163 placebo harm. *$p<0.001$ vs. placebo. †$p<0.01$ vs. placebo. MADRS = Montgomery–Åsberg Depression Rating Scale, NNH = number needed to harm, NNT = number needed to treat.

antidepressants in acute bipolar depression (with approximately 90% of patients having bipolar I disorder) included 416 patients taking antidepressants and 610 taking placebo (Sidor and MacQueen, 2011). However, 1 study (the olanzapine plus fluoxetine registration study) accounted for approximately 42% of these patients (Tohen et al., 2003) and another contributed approximately 32% of the patients (Sachs et al., 2007), so that the remaining 4 studies accounted for only approximately 26% of all patients (Amsterdam and Shults, 2005; Cohn et al., 1989; Nemeroff et al., 2001; Shelton and Stahl, 2004). In this meta-analysis, antidepressants had a favorable triple-digit NNH for TEAS of 200 (95% CI was NS); however, this was in the context of an unfavorable double-digit NNT of 29 (95% CI was also NS) (Figure 4, right) (Sidor and MacQueen, 2011). Thus, although antidepressants were numerically more likely to yield benefit (response) than harm (mood switch) compared with placebo, the favorable benefit/harm ratio was offset by inadequate efficacy. Not included in this meta-analysis was a recent multicenter, double-blind, placebo-controlled study in which paroxetine monotherapy (*N*=118) compared with placebo (*N*=121) similarly yielded a favorable double-digit NNH for TEAS of 56 (95% CI was NS), albeit in the context of an unfavorable double-digit NNT of 46 (95% CI was also NS; not illustrated) (McElroy et al., 2010).

Thus, lamotrigine and antidepressants, compared with the 2 older FDA-approved treatments for acute bipolar depression, both appeared to yield enhanced (adequate) tolerability at the cost of poorer (inadequate) efficacy.

## 6. Newer approved and emerging treatments for bipolar depression

In 2013, lurasidone received FDA approval for acute major depressive episodes in patients with bipolar I disorder (i.e., acute bipolar I depression), not only as monotherapy, but also as adjunctive therapy (added to lithium or valproate), based on adequately sized, multicenter, randomized, double-blind, placebo-controlled trials that demonstrated efficacy in acute bipolar depression in patients with bipolar I disorder (Loebel et al., 2014a; Loebel et al., 2014b).

Among adults with acute bipolar I depression, lurasidone monotherapy compared with placebo had an NNT for response of 5 (4–8) and an NNH for akathisia of 15 (10–33) (Figure 5, left) (Citrome et al., 2014; Loebel et al., 2014a). Therefore, lurasidone monotherapy compared with placebo was not only efficacious, but was more likely to yield benefit (response) than harm (akathisia). Additionally, lurasidone adjunctive therapy (added to lithium or valproate) compared with placebo had an NNT for response of 7 (4–24) and an NNH for nausea of 16 (95% CI was NS) (Figure 5, right) (Citrome et al., 2014; Loebel et al., 2014b). Thus, lurasidone adjunctive therapy compared with placebo was numerically (the 95% CIs for nausea was NS) more likely to yield benefit (response) than harm (nausea). Hence, lurasidone, whether administered as monotherapy or adjunctive therapy, appeared to have a favorable benefit/harm ratio that was not offset by reduction in efficacy, making lurasidone an important new treatment option for bipolar I depression.

Variable results have been presented for the low-affinity dopamine transporter inhibitor armodafinil. One adequately sized, multicenter, randomized, double-blind, placebo-controlled trial of adjunctive armodafinil therapy (added to FDA-approved bipolar maintenance treatments other than quetiapine) demonstrated efficacy for acute depression in patients with bipolar I disorder (Calabrese et al, 2014). However, a second such trial was negative (Frye et al., 2013), as was a third such trial (Adler et al., 2014; Frye et al., 2014).

In the first trial, in adults with acute bipolar I depression, adjunctive armodafinil therapy (added to lithium, valproate, olanzapine, risperidone, aripiprazole, or MS plus ziprasidone) compared with placebo had an NNT for response of 9 (5–43) and an NNH for anxiety of 29 (17–107) (Figure 6, left) (Calabrese et al., 2014). Thus, armodafinil adjunctive therapy compared with placebo was not only efficacious, but was numerically (the 95% CIs overlapped) more likely to yield benefit (response) than harm (anxiety). However, in the second and third acute bipolar

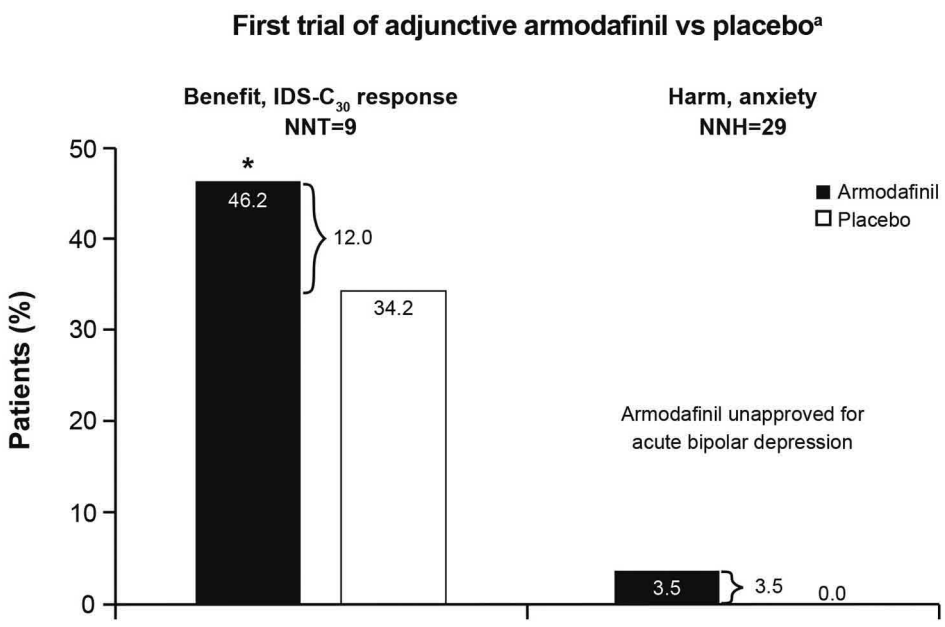


**Fig 6.** Benefits and harms of investigational bipolar depression treatment: adjunctive armodafinil. Number needed to treat (response) and number needed to harm (adverse effect rates). In the first (but not second or third) trial, armodafinil was superior to placebo and numerically more likely to yield benefit than harm compared with placebo. Dose of armodafinil was 150 mg/d. [a]Data from Calabrese et al, 2014, J. Clin. Psychiatry, published online ahead of print July 22, 2014; Number of patients, adjunctive armodafinil vs. placebo: *N*=197 armodafinil benefit, *N*=196 placebo benefit, *N*=198 armodafinil harm, *N*=199 placebo harm. **p*<0.05 vs. placebo. IDS-$C_{30}$ = 30 Item Inventory of Depressive Symptomatology–Clinician Rated, NNH = number needed to harm, NNT = number needed to treat.

**Table 2**
Benefits (NNTs) and harms (NNHs) of approved and unapproved bipolar depression treatments.

| Reference | Treatment | NNT (95% CI) | Side Effect | NNH (95% CI) | Benefit vs. Harm |
|---|---|---|---|---|---|
| | **Approved** | | | | |
| Tohen et al., 2003 | Olanzapine + fluoxetine | 4 (3–8) | ≥7% weight gain | 6 (4–10) | CIs overlap |
| Calabrese et al., 2005; Thase et al., 2006 | Quetiapine | 6 (5–9) | Sedation/somnolence | 5 (4–5) | CIs overlap |
| Loebel et al., 2014a | Lurasidone | 5 (4–8) | Akathisia | 15 (10–33) | Benefit>harm |
| Loebel et al., 2014b | Lurasidone (adjunctive) | 7 (4–24) | Nausea | 16 (NS) | NC |
| | **Unapproved** | | | | |
| Tohen et al., 2003 | Olanzapine (olanzapine + fluoxetine trial) | 12 (7–63) | ≥7% weight gain | 6 (5–7) | CIs overlap |
| Tohen et al., 2012 | Olanzapine (international trial) | 11 (6–1130) | ≥7% weight gain | 5 (4–6) | CIs overlap |
| Calabrese et al., 2008; Geddes et al., 2009 | Lamotrigine | 12 (8–41) | Sedation/somnolence | 37 (NS) | NC |
| Sidor and MacQueen, 2011 | Antidepressants (adjunctive) | 29 (NS) | TEAS | 200 (NS) | NC |
| McElroy et al., 2010 | Paroxetine | 46 (NS) | TEAS | 56 (NS) | NC |
| Calabrese et al., 2014 | Armodafinil (adjunctive) | 9 (5–43) | Anxiety | 29 (17–107) | CIs overlap |

CI = confidence interval; NC = not calculated (at least one 95% CI is NS); NNH = number needed to harm for specific side effect compared with placebo; NNT = number needed to treat for response compared with placebo; NS = non-significant (infinite/discontinuous) confidence interval; TEAS = treatment-emergent affective switch.

depression trials, adjunctive armodafinil compared with placebo did not demonstrate efficacy, although tolerability was adequate (Adler et al., 2014; Frye et al., 2014; Frye et al., 2013).

## 7. Limitations

NNT and NNH are categorical (rather than continuous) metrics. The use of NNH for risk assessment may be limited for rare, serious, and more chronic side effects. Also, selection of the specific side effect of greatest interest varies across patients, limiting the applicability of NNHs used in this study for individual patients. Use of efficacy (versus effectiveness) studies entails less generalizability.

## 8. Conclusion

Analysis of NNT and NNH data show that lamotrigine and antidepressants yield better tolerability, compared with the two older FDA-approved treatments for acute bipolar depression (olanzapine-fluoxetine combination and quetiapine monotherapy), but at the cost of inadequate efficacy (Table 2). In contrast, more recent data indicate that lurasidone as monotherapy and as adjunctive therapy had better tolerability compared with the two older FDA-approved bipolar depression treatments, without compromising efficacy. Therefore, lurasidone appears to be an important new treatment option for bipolar I depression. Finally, although adjunctive armodafinil has yielded better

tolerability compared with the two older FDA-approved bipolar depression treatments, its efficacy in bipolar I depression has not been consistently demonstrated.

Older FDA-approved bipolar depression treatments, such as the olanzapine-fluoxetine combination and quetiapine monotherapy, may still have utility in high-urgency situations, where a pressing clinical need for efficacy mitigates their tolerability shortcomings. In contrast, the older treatments lamotrigine and antidepressants, and possibly the newer treatment adjunctive armodafinil, none of which are approved for acute bipolar depression therapy, may have utility in low-urgency situations, in which a compelling need for tolerability might mitigate their efficacy shortcomings. Lurasidone may ultimately prove to have utility in a broad spectrum of situations, independent of the degree of urgency, because of evidence suggesting not only adequate efficacy, but also adequate tolerability.

**Disclosures**

NUVIGIL (armodafinil) is not indicated for the treatment of major depression associated with bipolar I disorder. Teva conducted three Phase III studies. Based on an evaluation of the totality of results from all three studies, Teva has ceased development of and will not proceed with regulatory filings for Nuvigil (armodafinil) for the treatment of major depression associated with bipolar I disorder.

**Conflict of interest**

Dr. Ketter has served as a consultant to Allergan, Avanir, Bristol-Myers Squibb, Cephalon (now Teva), Forest, Janssen, Merck, Sunovion, and Teva. He has received speaker fees from Abbott, AstraZeneca, GlaxoSmithKline, and Otsuka, and through Stanford University has received grants from AstraZeneca, Cephalon (now Teva), Lilly, Pfizer, and Sunovion. He received royalties from American Psychiatric Publishing. His spouse is employed by and owns stock in Janssen.

Dr. Miller received travel and accommodations compensation from the Agency for Healthcare Research and Quality for attendance at an investigators meeting in 2010. She also received a $1500 honorarium and travel and accommodations compensation from Pamlab, Inc. for attendance at an investigators meeting in 2011, and travel and accommodations compensation from Elan Pharmaceuticals for attendance at an investigators meeting in 2012.

Dr Dell'Osso has been a consultant and a speaker bureau member for AstraZeneca and has received grant/research support from Cyberonics, Inc., Bristol-Meyers Squibb, and Eli Lilly.

Dr. Calabrese has served as a consultant to or on advisory boards or speakers' bureaus for AstraZeneca, Benecke, Lundbeck, Medwiz Healthcare, Promedica, Spirant Communications Private Limitex, Biomedical Development Corporation, Elan Pharmaceuticals, Health & Wellness Partners, Hoffman LaRoche, Otsuka, Scientia, Sunovion, Takeda, Teva, Ohio Psychiatric Association, Ohio State University, University of Cincinnati, University of Toronto, Forest, Lilly Pharmaceuticals, CME Outfitters, Dainippon Sumitomo Pharma, Convergent Healthcare Solutions, American Foundation Suicide Prevention, Merck, and Pfizer. Dr. Calabrese has also received grant/research support from the NIMH, Sunovion, and Cephalon.

Dr. Frye has served on advisory boards for Janssen and Teva and as a consultant to Allergan, Merck, Mitsubishi Tanabe Pharma Co, Myriad, Sunovion, Takeda Global Research, and United BioSource. He has received grant support from Pfizer, Myriad, the National Institute of Mental Health (NIMH), the National Institute of Alcohol Abuse and Alcoholism (NIAAA), the National Alliance for Research on Schizophrenia and Depression (NARSAD) and the Mayo Foundation. He has developed CME presentations for Sanofi-Aventis and has received travel support from AstraZeneca, Bristol-Myers Squibb, CME Outfitter, GlaxoSmithKline, and Otsuka.

In the past 36 months, Dr. Citrome has engaged in collaborative research with or received consulting or speaking fees from Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly, Envivo, Forest, Genentech, Janssen, Lundbeck, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Shire, Sunovion, Takeda, and Valeant and owns a small number of shares of common stock in Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer.

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**Contributor's statement**

Terence Ketter designed the study. Terence Ketter and Shefali Miller managed the literature searches and performed the statistical analyses. Terence Ketter wrote the first draft of the manuscript. Shefali Miller, Bernardo Dell'Osso, Joseph Calabrese, Mark Frye, and Leslie Citrome critically reviewed and revised the manuscript. All authors contributed to and have approved the final manuscript.

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