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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.

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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