Demographic Variables, Design Characteristics, and Effect Sizes of Randomized, Placebo-Controlled, Monotherapy Trials of Major Depressive Disorder and Bipolar Depression

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ABSTRACT

Objective: The aim of this work is to compare the efficacy of pharmacologic agents for the treatment of major depressive disorder (MDD) and bipolar depression.

Data Sources: MEDLINE/PubMed databases were searched for studies published in English between January 1980 and September 2014 by cross-referencing the search term *placebo* with each of the antidepressant agents identified and with *bipolar*. The search was supplemented by manual bibliography review.

Study Selection: We selected double-blind, randomized, placebo-controlled trials of antidepressant monotherapies for the treatment of MDD and of oral drug monotherapies for the treatment of bipolar depression. 196 trials in MDD and 19 trials in bipolar depression were found eligible for inclusion in our analysis.

Data Extraction: Data were extracted by one of the authors and checked for accuracy by a second one. Data extracted included year of publication, number of patients randomized, probability of receiving placebo, duration of the trial, baseline symptom severity, dosing schedule, study completion rates, and clinical response rates.

Results: Response rates for drug versus placebo in trials of MDD and bipolar depression were 52.7% versus 37.5% and 54.7% versus 40.5%, respectively. The random-effects meta-analysis indicated that drug therapy was more effective than placebo in both MDD (risk ratio for response = 1.373; $P < .001$) and bipolar depression (risk ratio = 1.257; $P < .001$) trials. The meta-regression analysis suggested a statistically significant difference in the risk ratio of responding to drug versus placebo between MDD and bipolar depression trials in favor of MDD ($P = .008$).

Conclusions: Although a statistically significantly greater treatment effect size was noted in MDD relative to bipolar depression studies, the absolute magnitude of the difference was numerically small. Therefore, the present study suggests no clinically significant differences in the overall short-term efficacy of pharmacologic monotherapies for MDD and bipolar depression.

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Major depressive episodes (whether unipolar or bipolar) contribute to a significant illness burden in developing and developed nations. Major depressive disorder (MDD) is a highly prevalent and potentially debilitating illness, associated with significant disability, morbidity, and mortality, while, in bipolar disorder, major depressive episodes often contribute the majority of burden with respect to functional impairment, morbidity, mortality, and patient suffering.[1–5] Pharmacologic agents represent the mainstay of treatment for both MDD and bipolar depression. However, the treatment of bipolar depression remains one of the most challenging problems in modern clinical psychopharmacology. A meta-analysis[6] of randomized double-blind trials found that, of 8 medications studied, only olanzapine, quetiapine, and the combination of olanzapine and fluoxetine demonstrated higher remission rates than placebo in bipolar depression. More recently, lurasidone has also shown efficacy relative to placebo.[7] Similarly, in a more recent meta-analysis[8] of placebo-controlled monotherapy trials of various nonantidepressants agents for acute bipolar depression, the authors concluded that findings with olanzapine-fluoxetine, lurasidone, and quetiapine were encouraging, while lithium required adequate testing. On the other hand, despite the common use of antidepressants in the clinical management of bipolar depression, the controlled evidence of their efficacy is inconclusive, and the discussion of their effectiveness in bipolar depression is still ongoing and controversial. For example, a recent meta-analysis[9] found no significant difference between antidepressants and placebo in the treatment of bipolar depression.

Double-blind, randomized, placebo-controlled clinical trials are considered the "gold standard" for the development of novel pharmacotherapies in mood disorders. Unfortunately, in both MDD and bipolar depression, medications often fail to separate statistically from placebo in terms of efficacy, with substantial and highly variable placebo response rates rendering many studies uninformative. In addition, the substantial variability in placebo response rates across clinical trials in major depression poses a challenge with respect to comparing the efficacy of different treatments across studies. Over the past several years, however, a number of studies[10] have been published that have improved our ability to predict placebo response rates as well as treatment effect size as a function of study design and/or patient characteristics. Our group, for instance, has published 2 separate meta-analyses examining predictors of placebo response and

Clinical Points

- Major depressive episodes (whether unipolar or bipolar) are highly prevalent and associated with significant disability, morbidity, and mortality.
- Studies comparing the efficacy of pharmacologic treatments for major depressive disorder and bipolar depression are lacking.
- Our study suggests that there are no clinically significant differences in the overall short-term efficacy of pharmacologic monotherapies for major depressive disorder and bipolar depression.

drug-placebo differences in efficacy in both MDD[11] and bipolar depression.[12] While certain variables were found to hold predictive value in MDD or bipolar depression alone, the probability of receiving placebo as well as baseline illness severity predicted effect size in both bipolar depression and MDD trials. While a number of meta-analyses have sought to quantify the efficacy of pharmacologic agents in MDD[11] and bipolar depression,[6] analyses comparing the efficacy of these 2 treatment groups have not been conducted to date. The purpose of this work is to compare the efficacy of pharmacologic agents for bipolar depression versus MDD with the use of a meta-regression technique. To account for across-study variability, we controlled for the probability of receiving placebo as well as baseline illness severity, since these are the 2 variables found to predict treatment effect size in MDD and bipolar depression.

METHODS

Data Sources and Search Strategy

We sought to identify double-blind, randomized, placebo-controlled trials of (1) antidepressants used as monotherapy for the treatment of MDD and (2) oral drugs used as monotherapy (ie, not in conjunction with agents with known antimanic or antidepressant properties) for the treatment of bipolar depression for possible inclusion in the meta-analysis. As antidepressants, we defined pharmacologic agents that have or had, at one point, received a letter of approval by the US, Canadian, Japanese, Australian, or EU drug regulatory agencies for the treatment of MDD. Eligible studies were first identified by searching PubMed, cross-referencing the search term *placebo* with each of the antidepressant agents as defined above, then cross-referencing the search term *placebo* with *bipolar*. The search was limited to articles that were published between January 1, 1980, and September 1, 2014 (inclusive). The year 1980 was used as a cutoff in order to decrease diagnostic variability, since the *DSM-III* was introduced in 1980.[13] To expand our database, we then reviewed the reference list of all studies identified with PubMed/MEDLINE. The final inclusion of articles was determined by consensus between the authors.

Study Selection

We selected randomized, double-blind, placebo-controlled trials that met all of the following criteria: the studies (1) defined MDD and bipolar depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition,[13] Third Edition-Revised,[14] Fourth Edition,[15] or Fifth Edition[16]) research diagnostic criteria,[17] or Feighner Diagnostic Criteria[18]; (2) had a minimum duration of 4 weeks of double-blind treatment; (3) focused on the use of drugs in their oral formulation; (4) presented entirely original (not previously published) data; (5) focused on the treatment of adult patients; (6) did not exclusively focus on the treatment of patients with comorbid alcohol or substance use disorders, patients with a specific comorbid medical illness, or patients with other affective disorders, including MDD with psychotic features, dysthymic disorder, neurotic depression, minor depression, hypomania, or mania; and (7) involved the use of the Hamilton Depression Rating Scale (HDRS),[19] the Montgomery-Asberg Depression Rating Scale (MADRS),[20] or the Clinical Global Impressions-Improvement scale[21] as one of their outcome measures.

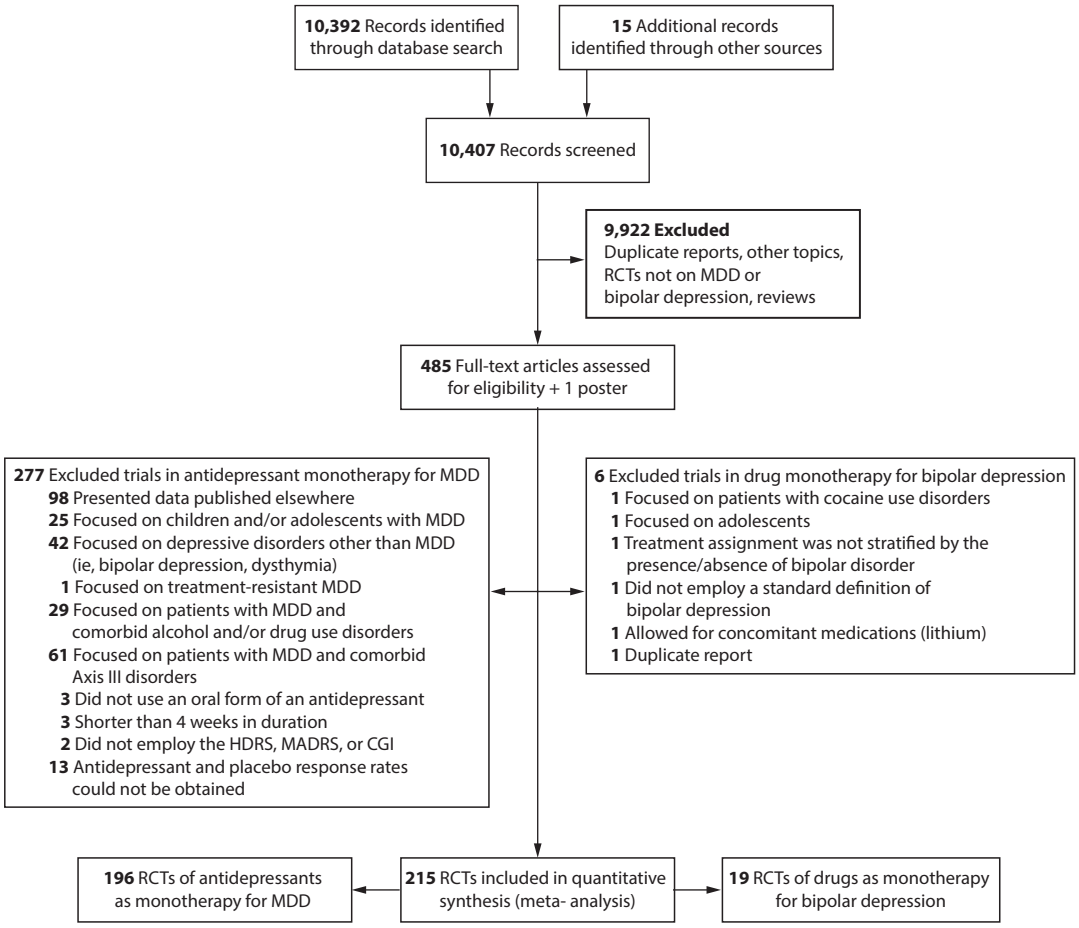
Data Extraction

Data were extracted by one of the authors and checked for accuracy by a second one. Data extracted included year of publication, number of patients randomized, probability of receiving placebo, duration of the trial, baseline symptom severity, dosing schedule, study completion rates, and clinical response rates. Clinical response was defined as a 50% or greater reduction in HDRS or MADRS scores, baseline to end point, or a CGI-I score < 3 at the final visit. For consistency, the HDRS was chosen over the MADRS or CGI when response rates from multiple scales were reported. For studies that reported only CGI-based response rates, the HDRS-based response rates were either obtained from the sponsor or imputed using the method of Walsh et al.[22] In cases where continuous (change in depression severity scores), but not dichotomous (response rates), outcomes were presented, and dichotomous outcomes could not be obtained from the study authors, we converted continuous outcomes to dichotomous outcomes using the method described in Iovieno et al.[23] When the baseline severity was reported only with the MADRS, these scores were converted to HDRS-equivalent scores by multiplying with a factor of 0.7524, calculated based on data from the study by Carmody et al.[24] For consistency, we used the intent-to-treat (ITT)–based response rates or the modified ITT–based response rates ("efficacy sample") in the present analysis. Whenever ITT-based response rates were not available in the publication and were not obtainable by the sponsor, we utilized response rates based on completers. The probability of receiving placebo was computed from the number of treatment arms and the randomization schedule of each trial. For example, a 2-arm trial with a 2:1 randomization favoring active treatment yields a 1 in 3 chance of receiving placebo.

Quantitative Data Synthesis

Random-effects meta-analysis was utilized to estimate the pooled risk ratio of responding to active treatment versus placebo in the monotherapy trials for MDD and bipolar

Figure 1. Flow Diagram: Trial Identification and Selection Process



Abbreviations: CGI = Clinical Global Impressions, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, RCT = randomized controlled trial.

depression. A meta-regression was used to compare the risk ratio of responding to the active drug versus placebo between MDD and bipolar depression trials. This meta-regression was first conducted without covariates. Subsequently, severity at baseline and the probability of being randomized to placebo were entered as covariates since they had previously been found to influence the risk ratio of clinical response following drug versus placebo therapy in both MDD[11] and bipolar depression[12] trials. All tests conducted were 2-tailed, with α set at the .05 level.

RESULTS

Initially, 10,392 abstracts were identified in PubMed/MEDLINE. Of these, 9,922 were excluded (other topics, reviews, duplicate reports). Abstracts for the remaining 470 clinical trials (either trials of antidepressants used as monotherapy for MDD or trials of medications used as monotherapy for bipolar depression) were obtained and reviewed. Fifteen additional articles were identified after reviewing the reference lists of the articles and 4 large reviews and meta-analyses. Moreover, a poster of a monotherapy study in bipolar depression not yet published was identified at a large scientific meeting and included. Of the 485 potential articles (plus 1 poster), 283 were excluded for reasons listed in Figure 1.

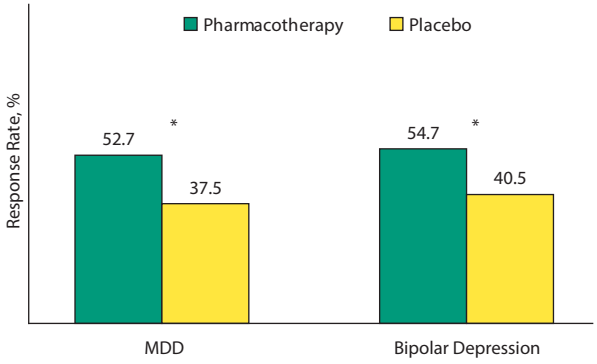
A total of 202 articles and 1 poster were found eligible for inclusion in our pooled analysis (189 articles focusing on antidepressant monotherapy in MDD and 13 articles and 1 poster focusing on drug monotherapy in bipolar depression). One hundred eighty-four of the 189 articles on antidepressant monotherapy for MDD reported the results of a single trial, while 5 reported results of several (a total of 12) trials. Ten of the 13 articles on drug monotherapy for bipolar depression and the poster reported the results of a single trial, while 3 reported results of several (a total of 9) trials. The results of 1 of these trials were reported twice. Therefore, we pooled a total of 342 antidepressant versus placebo comparisons from 196 antidepressant monotherapy trials for MDD (56,133 patients randomized to an antidepressant [n = 35,751] versus placebo [n = 20,382]) and 28 drug versus placebo comparisons from 19 drug monotherapy trials for bipolar depression (7,191 patients randomized to an active treatment [n = 4,482] vs placebo [n = 2,709]) (Table 1).

Table 1. Characteristics of the Trials for MDD and for Bipolar Depression

Characteristic	MDD (196 trials)		Bipolar Depression (19 trials)	
No. of drug-placebo comparisons	342		28	
Year of publication, mean (±SD)	1998 (±9 y)		2008 (±3 y)	
Sample size, mean±SD, n	104±63		158±80	
Duration, mean±SD, wk	7.2±2.8		7.4±1.1	
HDRS-17 score (severity at baseline), mean±SD	22.0±3.8		23.3±1.4	
Probability of receiving placebo, mean±SD	0.35±0.1		0.40±0.1	
Trials with probability of receiving placebo <0.5, %	76.0		47.4	
Fixed-dosing scheme, %	33.7		15.8	
	Drug	Placebo	Drug	Placebo
Response rate, %	52.7	37.5	54.7	40.5
Completion rate, %	72.7	71.8	64.2	63.0

Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, MDD = major depressive disorder.

Figure 2. Response Rates in Randomized Controlled Trials of Major Depressive Disorder (MDD) Versus Bipolar Depression



*P < .001.

Specific descriptions of the 19 bipolar depression trials are reported in Table 2.

The unadjusted meta-regression analysis suggested a statistically significant difference in the risk ratio of responding to active drug versus placebo between MDD and bipolar depression trials in favor of the former type (coefficient = −0.106, P = .008). Similarly, the adjusted meta-regression analysis suggested a statistically significant difference in the risk ratio of responding to active drug versus placebo between MDD and bipolar depression trials in favor of the former type (coefficient = −0.116, P = .005). Response rates for antidepressants versus placebo in clinical trials of MDD were 52.7% (18,862/35,751 patients) versus 37.5% (7,642/20,382 patients), respectively (Figure 2). Response rates for active treatment versus placebo in clinical trials of bipolar depression were 54.7% (2,559/4,680 patients) versus 40.5% (1,116/2,754 patients), respectively (Figure 2). The result of the random-effects meta-analysis indicated that drug therapy resulted in statistically significantly higher response rates relative to placebo in both MDD trials (risk ratio = 1.373; 95% CI, 1.351–1.396; P < .001) and bipolar depression trials (risk ratio = 1.257; 95% CI, 1.185–1.335; P < .001). Statistically significant evidence for heterogeneity was found in the risk ratio for response to active drug versus placebo in both MDD trials (Q_{341} = 693.827, P < .001) and bipolar depression trials (Q_{27} = 45.263, P = .010). The number needed to treat (NNT) was approximately 7 in both MDD trials and bipolar depression trials.

Table 2. Characteristics of Placebo-Controlled, Randomized, Monotherapy Trials in Bipolar Depression

Study	Duration, wk	Treatment Arm	Sample Size, n
Calabrese et al,[25] 1999	7	Lamotrigine (200 mg)	63
		Lamotrigine (50 mg)	66
		Placebo	66
Tohen et al,[26] 2003	8	Olanzapine (5–20 mg)	370
		Placebo	377
Calabrese et al,[27] 2005	8	Quetiapine (600 mg)	180
		Quetiapine (300 mg)	181
		Placebo	181
Thase et al,[28] 2006	8	Quetiapine (600 mg)	169
		Quetiapine (300 mg)	172
		Placebo	168
Ghaemi et al,[29] 2007	6	Divalproex XR (70–90 ng/dL)	9
		Placebo	9
Calabrese et al,[30] 2008 (4 trials)	10	Lamotrigine (100–400 mg)	103
		Placebo	103
	8	Lamotrigine (200 mg)	133
		Placebo	124
	8	Lamotrigine (200 mg)	111
		Placebo	110
	8	Lamotrigine (200 mg)	131
		Placebo	128
Thase et al,[31] 2008 (2 trials)	8	Aripiprazole (5–30 mg)	186
		Placebo	188
	8	Aripiprazole (5–0 mg)	187
		Placebo	188
McElroy et al,[32] 2010	8	Quetiapine (600 mg)	232
		Quetiapine (300 mg)	229
		Paroxetine (20 mg)	118
		Placebo	121
Suppes et al,[33] 2010	8	Quetiapine XR (300 mg)	139
		Placebo	138
Young et al,[34] 2010	8	Quetiapine (600 mg)	205
		Quetiapine (300 mg)	200
		Lithium (600–1800 mg)	102
		Placebo	95
Muzina et al,[35] 2011	6	Divalproex (1–2 g)	26
		Placebo	28
Tohen et al,[36] 2012	6	Olanzapine (5–20 mg)	343
		Placebo	171
Loebel et al,[37] 2013	6	Lurasidone (80–120 mg)	162
		Lurasidone (20–60 mg)	161
		Placebo	162
Lombardo et al,[38] 2012 (2 trials)	6	Ziprasidone (40–80 mg)	158
		Ziprasidone (120–160 mg)	166
		Placebo	162
	6	Ziprasidone (40–160 mg)	180
		Placebo	190

Abbreviation: XR = extended release.

DISCUSSION

The present meta-regression is the first to compare the effect size seen during the acute phase of pharmacotherapy

for MDD and bipolar depression. Interestingly enough, even though a statistically significantly greater treatment effect size was noted in MDD than in bipolar depression studies (risk difference for response of 15.2% vs 14.2%), the absolute magnitude of the difference (1%) is, numerically, small and clinically insignificant. In fact, the NNT for response for pharmacotherapies administered as monotherapy versus placebo in MDD and bipolar depression was approximately 7—clearly below the threshold of 10, which is considered the threshold for clinical significance. This finding probably reflects the lack of major differences in study characteristics found to predict effect size both in MDD and in bipolar depression placebo-controlled trials (ie, baseline illness severity and the probability of receiving placebo). The present finding is of great importance for clinical practice, since it confirms that, at least with respect to short-term treatment efficacy, patients who present with either bipolar depression or MDD have equal chances of experiencing significant improvement during the course of treatment. Thus, with respect to short-term treatment outcome, neither of the 2 types of major mood disorders confers a particularly worse prognosis—often a concern of patients when first receiving a diagnosis of major depressive disorder.

Several limitations should be taken into account when taking the present findings into consideration. First, it is important to keep in mind that the majority of studies focusing on the pharmacotherapy of bipolar depression involves the enrollment of patients with type bipolar I disorder, making it difficult, at this point in time, to examine whether more subtle differences exist when comparing MDD with bipolar I versus bipolar II disorder. Second, as can be seen in Table 1, the overall adherence of patients with MDD versus bipolar depression in their respective clinical trials differs. It is possible that differences in efficacy would have been observed were adherence rates more similar between the 2 types of patient populations. Furthermore, whether long-term differences in efficacy exist cannot be examined using the present dataset. Future studies will be needed to address these and other important clinical questions.

In summary, the present study does not suggest any clinically significant differences in the overall short-term efficacy of pharmacologic monotherapies for MDD and bipolar depression. Upon receiving a first lifetime diagnosis of major depression, patients should be informed that the type of illness—whether unipolar or bipolar—does not seem to influence acute efficacy. Whether longer-term differences in efficacy exist should be examined in separate studies.

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Drug names: aripiprazole (Abilify and others), divalproex (Depakote and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lurasidone (Latuda), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel and others), ziprasidone (Geodon and others).

Potential conflicts of interest: **Dr Papakostas** has served as a consultant for Abbott, AstraZeneca, Avanir, Brainsway, Bristol-Myers Squibb, Cephalon, Dey, Eli Lilly, Genentech, GlaxoSmithKline, Evotec AG, H. Lundbeck A/S, Inflabloc, Jazz, Novartis AG, Otsuka, PAMLAB, Pfizer, Pierre Fabre Laboratories, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire, Sunovion, Takeda, Theracos, and Wyeth; has received honoraria from Abbott, AstraZeneca, Avanir, Bristol-Myers Squibb, Brainsway, Cephalon, Dey, Eli Lilly, Evotec AG, GlaxoSmithKline, Inflabloc, Jazz, H. Lundbeck A/S, Meiji Seika, Novartis AG, Otsuka, PAMLAB, Pfizer, Pierre Fabre Laboratories, Ridge Diagnostics, Shire, Sunovion, Takeda, Theracos, Titan, and Wyeth; has received research support from AstraZeneca, Bristol-Myers Squibb, Forest, the National Institute of Mental Health (NIMH), PAMLAB, Pfizer, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sunovion, and Theracos; and has served (not currently) on the speaker's bureau for Bristol-Myers Squibb and Pfizer. **Dr Fava** has received research support from Abbot, Alkermes, American Cyanamid, Aspect Medical Systems, AstraZeneca, Avanir, BioResearch, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Clintara, Covance, Covidien, Eli Lilly, EnVivo, Euthymics Bioscience, Forest, Ganeden Biotech, GlaxoSmithKline, Harvard Clinical Research Institute, Hoffman-LaRoche, Icon Clinical Research, i3 Innovus/Ingenix, Janssen R&D, Jed Foundation, Johnson & Johnson Pharmaceutical Research & Development, Lichtwer Pharma GmbH, Lorex, Lundbeck, MedAvante, Methylation Sciences, National Alliance for Research on Schizophrenia & Depression (NARSAD), National Center for Complementary and Alternative Medicine (NCCAM), National Institute of Drug Abuse (NIDA), NIMH, Neuralstem, Novartis AG, Organon, PamLab, Pfizer, Pharmacia-Upjohn, Pharmaceutical Research Associates, Pharmavite, PharmoRx Therapeutics, Photothera, Reckitt Benckiser, Roche, RCT Logic (formerly Clinical Trials Solutions, LLC), Sanofi-Aventis US, Shire, Solvay Pharmaceuticals, Stanley Medical Research Institute, Synthelabo, and Wyeth-Ayerst; has been an advisor/consultant to Abbott, Affectis AG, Alkermes, Amarin, Aspect Medical Systems, AstraZeneca, Auspex, Bayer AG, Best Practice Project Management, BioMarin, Biovail, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Cerecor, CNS Response, Compellis, Cypress, DiagnoSearch Life Sciences (P), Dainippon Sumitomo, Dov, Edgemont, Eisai, Eli Lilly, EnVivo, ePharmaSolutions, EPIX, Euthymics Bioscience, Fabre-Kramer, Forest, GenOmind, GlaxoSmithKline, Grunenthal GmbH, i3 Innovus/Ingenis, Janssen, Jazz, Johnson & Johnson Pharmaceutical Research & Development, Knoll, Labopharm, Lorex, Lundbeck, MedAvante, Merck, MSI Methylation Sciences, Naurex, Neuralstem, Neuronetics, NextWave, Novartis AG, Nutrition 21, Orexigen Therapeutics, Organon, Otsuka, Pamlab, Pfizer PharmaStar, Pharmavite, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa, Puretech Ventures, PsychoGenics, Psylin Neurosciences, RCT Logic (formerly Clinical Trials Solutions, LLC), Rexahn, Ridge Diagnostics, Roche, Sanofi-Aventis US, Sepracor, Servier Laboratories, Schering-Plough, Solvay, Somaxon, Somerset, Sunovion, Supernus, Synthelabo, Takeda, Tal Medical, Tetragenex, TransForm, Transcept, and Vanda; has received speaking/publishing support from Adamed, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cephalon, CME Institute/Physicians Postgraduate Press, Eli Lilly, Forest, GlaxoSmithKline, Imedex, Massachusetts General Hospital (MGH) Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis AG, Organon, Pfizer, PharmaStar, United BioSource, and Wyeth-Ayerst; has received equity holdings from Compellis and PsyBrain; has received a patent for Sequential Parallel Comparison Design, which is licensed by MGH to Pharmaceutical Product Development; holds a patent application for a combination of ketamine plus scopolamine in major depressive disorder; and receives copyright royalties for the MGH Cognitive & Physical Functioning Questionnaire, Sexual Functioning Inventory, Antidepressant Treatment Response Questionnaire, Discontinuation-Emergent Signs & Symptoms, and SAFER and from Lippincott Williams & Wilkins, Wolkers Kluwer, World Scientific Publishing. **Dr Iovieno** and **Mr Martinson** have no conflicts of interest to report.

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REFERENCES

1. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry*. 2002;59(6):530–537.
2. Judd LL, Akiskal HS, Schettler PJ, et al. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study. *Arch Gen Psychiatry*. 2005;62(12):1322–1330.
3. Kupka RW, Altshuler LL, Nolen WA, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*. 2007;9(5):531–535.
4. Calabrese JR, Hirschfeld RM, Reed M, et al. Impact of bipolar disorder on a US community sample. *J Clin Psychiatry*. 2003;64(4):425–432.

5. Goldberg JF, Harrow M. A 15-year prospective follow-up of bipolar affective disorders: comparisons with unipolar nonpsychotic depression. *Bipolar Disord*. 2011;13(2):155–163.
6. Vieta E, Locklear J, Günther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. *J Clin Psychopharmacol*. 2010;30(5):579–590.
7. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014;171(2):169–177.
8. Selle V, Schalkwijk S, Vázquez GH, et al. Treatments for acute bipolar depression: meta-analyses of placebo-controlled, monotherapy trials of anticonvulsants, lithium and antipsychotics. *Pharmacopsychiatry*. 2014;47(2):43–52.
9. Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. *J Clin Psychiatry*. 2011;72(2):156–167.
10. 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.
11. 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.
12. Nierenberg AA, Østergaard SD, Iovieno N, et al. Predictors of placebo response in bipolar depression. *Int Clin Psychopharmacol*. 2015;30(2):59–66.
13. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Third Edition. Washington, DC: American Psychiatric Association; 1980.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Third Edition Revised. Washington, DC: American Psychiatric Association; 1987.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
17. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35(6):773–782.
18. Feighner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26(1):57–63.
19. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
20. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
21. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
22. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.
23. Iovieno N, Tedeschini E, Bentley KH, et al. Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry*. 2011;72(8):1144–1151.
24. Carmody TJ, Rush AJ, Bernstein I, et al. The Montgomery Asberg and the Hamilton ratings of depression: a comparison of measures. *Eur Neuropsychopharmacol*. 2006;16(8):601–611.
25. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry*. 1999;60(2):79–88.
26. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079–1088.
27. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162(7):1351–1360.
28. Thase ME, Macfadden W, Weisler RH, et al; BOLDER II Study Group. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol*. 2006;26(6):600–609.
29. Ghaemi SN, Gilmer WS, Goldberg JF, et al. Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. *J Clin Psychiatry*. 2007;68(12):1840–1844.
30. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord*. 2008;10(2):323–333.
31. Thase ME, Jonas A, Khan A, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. *J Clin Psychopharmacol*. 2008;28(1):13–20.
32. McElroy SL, Weisler RH, Chang W, et al; EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry*. 2010;71(2):163–174.
33. Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J Affect Disord*. 2010;121(1–2):106–115.
34. Young AH, McElroy SL, Bauer M, et al; EMBOLDEN I (Trial 001) Investigators. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71(2):150–162.
35. Muzina DJ, Gao K, Kemp DE, et al. Acute efficacy of divalproex sodium versus placebo in mood stabilizer-naive bipolar I or II depression: a double-blind, randomized, placebo-controlled trial. *J Clin Psychiatry*. 2011;72(6):813–819.
36. Tohen M, McDonnell DP, Case M, et al. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. *Br J Psychiatry*. 2012;201(5):376–382.
37. Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy for the treatment of bipolar I depression: results of the 6-week, double-blind, placebo-controlled study (PREVAIL-2). Poster presented at the 165th Annual Meeting of the American Psychiatric Association; May 5–9, 2012; Philadelphia, PA
38. Lombardo I, Sachs G, Kolluri S, et al. Two 6-week, randomized, double-blind, placebo-controlled studies of ziprasidone in outpatients with bipolar I depression: did baseline characteristics impact trial outcome? *J Clin Psychopharmacol*. 2012;32(4):470–478.