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Brief communication (Original)

Long-term aripiprazole effectiveness in bipolar disorder patients decreases with pharmacotherapeutic complexity and degree of baseline mood disturbance

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Background: Aripiprazole, a second-generation antipsychotic, has been shown to have short- and long term efficacy in bipolar disorder as monotherapy and in two-drug combinations. However, its long-term effectiveness among patients with different degrees of pharmacotherapeutic complexity and baseline mood disturbances is not known.
Objective: To assess long-term aripiprazole effectiveness in bipolar disorder (BD) patients in relationship to pharmacotherapeutic complexity and degree of baseline mood disturbance.
Methods: Outpatients assessed with the Systematic Treatment Enhancement Program for BD (STEP-BD) Affective Disorders Evaluation, and monitored with the STEP-BD Clinical Monitoring Form received open-label aripiprazole.
Results: Ninety-seven patients (52 BDI, 40 BDII, 5 BD NOS, mean age 40.2 years, 75.3% female) received aripiprazole combined with a mean ± SD (median) of 2.9 ± 1.7 (3) other prescription psychotropics, with 39.2% (38/97) receiving up to triple-pharmacotherapy (aripiprazole plus up to 2 other psychotropics) and 60.8% (59/97) taking quadruple-or-more-pharmacotherapy (aripiprazole plus at least 3 other psychotropics). At baseline 71.1% (69/97) of patients were symptomatic and 28.9% (28/97) were euthymic. Overall, mean (median) aripiprazole final dose and duration were 17.6 (15) mg/day and 388 (190) days, respectively. Aripiprazole was discontinued in only one-quarter of euthymic patients taking up to triple-pharmacotherapy, but in two-thirds of other patients (symptomatic patients taking up to triple-pharmacotherapy and symptomatic/euthymic patients taking quadruple-or-more-pharmacotherapy).
Conclusion: Aripiprazole treatment of bipolar disorder may be modestly extended beyond mono-pharmacotherapy and dual-pharmacotherapy to include triple-pharmacotherapy in euthymic patients, but further extension beyond current indications may not be effective in most patients.

Keywords: Aripiprazole, bipolar disorder, effectiveness, treatment

Bipolar disorder is a serious psychiatric illness that in its broadest sense affects up to 4% of the population, causing recurrent and debilitating episodes of depression as well as recurrent, variably debilitating episodes of mood elevation [1]. The World Health Organization has ranked bipolar disorder as the ninth leading cause of disability adjusted life years in 15–44-year-old individuals [2]. Although the last decade has seen important advances in the pharmacotherapy of bipolar disorder, there remain substantial unmet needs in the management of this illness [3, 4]. For example, complicated combination pharmacotherapies are increasingly necessary to manage patients with more challenging forms of bipolar disorder [5], yet there are very few studies to inform this practice [6].

Aripiprazole is a second-generation antipsychotic that in controlled efficacy studies has antimanic properties [3, 4]. Hence, aripiprazole was significantly more efficacious than placebo in patients with acute mania, both as mono-pharmacotherapy [7-9] and as dual-pharmacotherapy (added to lithium or valproate) [10]. Aripiprazole was also significantly more efficacious than placebo in maintenance treatment

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in patients with bipolar I disorder with recent mania as mono-pharmacotherapy [11, 12] and as dual-pharmacotherapy (added to lithium or valproate) [13]. In contrast, aripiprazole monotherapy did not appear efficacious for acute bipolar I depression [14] and may lack a preventive antidepressant effect in patients with bipolar I disorder as mono-pharmacotherapy [11] or as dual-pharmacotherapy (added to lithium or valproate) [13]. Similarly, in a small pilot study, adding aripiprazole for 6 weeks was no better than adding placebo in bipolar I or II disorder patients who remained depressed despite taking a mood stabilizer (lithium or valproate) plus citalopram [15], and aripiprazole plus valproate only tended to be superior to placebo plus valproate in preventing depressive recurrence in bipolar I disorder patients with recent mixed episodes [16]. Nevertheless, occasional patients with bipolar depression resistance even to combination therapy may respond to adjunctive aripiprazole [17].

Although efficacy studies have informed treatment with aripiprazole of bipolar disorder patients with less complex illness and treatment regimens, there remains a lack of effectiveness studies to adequately inform the use of aripiprazole when treating more complicated patients encountered in clinical practice. Indeed, although as many as 1 in 5 individuals with bipolar disorder may be taking complex pharmacotherapy involving at least 4 medications [6], there is a lack of systematic assessment of aripiprazole effectiveness when administered in such regimens. We used an observational design and a sample of bipolar disorder outpatients who were primarily already receiving combination pharmacotherapy and who also commonly had comorbid conditions, to assess long-term aripiprazole effectiveness in relationship to pharmacotherapeutic complexity and degree of baseline mood disturbance in such challenging forms of bipolar disorder.

Methods

Bipolar disorder outpatients treated at the Stanford University Bipolar Disorders Clinic were assessed with the Systematic Treatment Enhancement for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation, and monitored longitudinally with the STEP-BD Clinical Monitoring Form [18, 19], as they received treatment guided by model practice procedures, which included published pharmacotherapy guidelines [19, 20]. This research was approved by the Stanford University Administrative Panel on Human Subjects, and patients provided verbal and written informed consent prior to participation. We assessed patients in whom open-label aripiprazole was naturalistically combined with other pharmacotherapies (including no other pharmacotherapy) between December 1, 2002 and February 28, 2010.

The primary effectiveness measure was the aripiprazole discontinuation rate. The secondary effectiveness measure was the rate of addition of subsequent psychotropic medications. Aripiprazole trial complexity was dichotomized by considering trials of up to triple-pharmacotherapy (aripiprazole added to up to two other prescription psychotropic medications) and quadruple-or-more-pharmacotherapy (aripiprazole added to at least three other prescription psychotropic medications).

Clinical status for syndromal depression and mood elevation was based upon criteria in the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [21]. Subsyndromal depression and mood elevation were defined as having more than two threshold DSM-IV-TR symptoms of either polarity, but not meeting DSM-IV-TR criteria for a syndromal mood episode, while euthymia comprised having no more than two threshold DSM-IV-TR symptoms of either polarity [18]. Symptomatic and euthymic patients were defined, respectively, as those having or lacking syndromal or subsyndromal depressive and/or mood elevation symptoms at first visit.

Descriptive statistics were compiled. Continuous measures were compared with paired and unpaired *t* tests and for non-normally distributed parameters with corresponding nonparametric tests (Wilcoxon sign rank and Mann–Whitney *U* tests), as indicated. Categorical parameters were compared with χ^2 and Fisher's exact tests, as indicated. Relationships between continuous parameters were assessed with parametric (Pearson) and nonparametric (Spearman rank) correlations, as indicated. A significance threshold of $p < 0.05$ was used, with no correction for multiple comparisons.

Results

Sample description and baseline characteristics

Ninety-seven (59 quadruple-or-more-pharmacotherapy and 38 up to triple-pharmacotherapy; 69 symptomatic and 28 euthymic) bipolar disorder outpatients underwent aripiprazole trials. Patients taking quadruple-or-more-pharmacotherapy compared with up to triple-pharmacotherapy were more often

symptomatic at baseline (79.7% vs. 57.9%, $\chi^2 = 5.3$, df = 1, Fisher's exact test $p = 0.038$) and had higher rates of lifetime history comorbid psychiatric (81.4% vs. 57.9%, post hoc $\chi^2 = 6.3$, df = 1, Fisher's exact test $p = 0.019$), and anxiety (62.7% vs. 39.5%, post hoc $\chi^2 = 5.0$, df = 1, Fisher's exact test $p = 0.037$) disorders (indicated by * in **Table 1**), but were statistically similar for all other parameters. Symptomatic compared with euthymic patients had a higher rate of lifetime history of alcohol use disorder (40.6% vs. 17.9%, post hoc $\chi^2 = 4.6$, df = 1, Fisher's exact test $p = 0.036$, indicated by ** in **Table 1**), but were statistically similar for all other parameters. Among symptomatic patients, aripiprazole was more often started when patients had depressive compared with mood elevation symptoms (in 69.6% and 30.4%, respectively). Indeed, 40.6% (28/69) of symptomatic patients in the current report were included in our earlier report of adjunctive aripiprazole in treatment-resistant bipolar depression [17], and did not differ significantly from the other 69 patients in the current report for the parameters.

Aripiprazole was started at Stanford in 80 patients, and prior to Stanford in 17 patients, with these groups being statistically similar for complexity of pharmacotherapy and for all demographic and illness characteristic parameters, with the exceptions (indicated by *** in **Table 1**) that patients with trials started at versus prior to Stanford had older current age (42.7 vs. 28.2 years, $t = 3.9$, df = 95 $p < 0.0001$), lower rate of some college education (30.0% vs. 64.7%, post hoc $\chi^2 = 7.3$, df = 1, Fisher's exact test $p = 0.01$), higher rate of any lifetime comorbid psychiatric disorder (77.5% vs. 47.1%, post hoc $\chi^2 = 6.5$, df = 1, Fisher's exact test $p = 0.017$), and longer illness duration (22.0 vs. 12.0 years, $t = 2.8$, df = 95 $p = 0.007$). The pattern of findings for patients starting aripiprazole prior to as opposed to at Stanford overlapped, so that pooled data are presented.

Table 1. Sample description (N = 97)

Item	Mean ± SD or number (%)
Age (years)***	40.2 ± 15.0
Female	75.3%
Race/ethnicity	
Asian	12.4%
Black	2.1%
Hispanic	44.1%
White	80.4%
Unspecified	1.0%
Marital status	
Single	40.2%
Married	47.4%
Divorced	8.2%
Living as married	1.0%
Widow(er)	3.1%
Education	
High school	12.4%
Some college***	36.1%
College degree	28.9%
Graduate degree	22.7%
Employment	
Full time	32.0%
Part time	10.3%
Unemployed	40.2%
Disabled	9.3%
Retired	8.2%
Diagnosis	
Bipolar I	53.6%
Bipolar II	41.2%
Bipolar NOS	5.2%

Table 1. Sample description (N = 97) (Continue)

Item	Mean ± SD or number (%)
Lifetime comorbidity	
Any psychiatric disorder*,***	72.2%
Any anxiety disorder*	53.6%
Alcohol use disorder**	34.0%
Substance use disorder	33.0%
Personality disorders	5.2%
Eating disorders	10.3%
Illness characteristics	
Onset age (years)	20.0 ± 11.3
Illness duration (years)***	19.9 ± 13.5
History of psychosis	49.5%
History of psychiatric hospitalization	47.4%
Rapid cycling ever	44.3%
Rapid cycling prior year	17.5%

Items with statistically significant differences for patients –, *Taking quadruple-or-more-pharmacotherapy (n = 59) compared with up to triple-pharmacotherapy (n = 38), **Baseline mood symptoms (n = 69) vs. euthymia (n = 28), ***Starting aripiprazole at (n = 80) compared with prior to (n = 17) Stanford.

Concurrent medications and aripiprazole dosing

Aripiprazole was combined with a mean ± SD (median) of 2.9 ± 1.7 (3) other prescription psychotropics and 1.1 ± 1.5 (1) prescription nonpsychotropic medications. Noted is that 60.8% (59/97) of trials were quadruple-or-more-pharmacotherapy (aripiprazole plus at least three concurrent prescription psychotropics), and 38/97 (39.2%) were up to triple-pharmacotherapy (aripiprazole plus up to two concurrent prescription psychotropics).

Patients taking quadruple-or-more-pharmacotherapy compared with up to triple-pharmacotherapy had a significantly higher mean number of concurrent baseline psychotropic (4.1 ± 1.0 vs. 1.2 ± 0.8, t = –15.2, df = 95, p < 0.0001), but not nonpsychotropic (1.2 ± 1.4 vs. 1.0 1.6, U = 935.0 z = –1.5, p = 0.141) prescription medications, and significantly higher rates of taking mood stabilizers, lamotrigine, lithium, (but not valproate) other anticonvulsants, second-generation antipsychotics, antidepressants, and hypnotics/benzodiazepines (**Table 2**).

Table 2. Baseline concurrent medications

	All patients (N =97)	≥Quadruple pharmacotherapy (n = 59)	≤Triple pharmacotherapy (n = 38)	*p*
Number of other prescription psychotropic medications, mean ± SD (median)	2.9 ± 1.7 (3)	4.1 ± 1.0 (4)	1.2 ± 0.8 (1)	<0.0001
Any mood stabilizer (%)	80.4%	91.5%	63.2%	0.001
Lamotrigine (%)	48.4%	64.4%	23.7%	0.0001
Lithium (%)	33.0%	44.1%	15.8%	0.004
Valproate (%)	16.5%	20.3%	10.5%	0.27
Other anticonvulsants (%)	23.7%	37.3%	2.6%	<0.0001
Second generation antipsychotics (%)	52.6%	67.8%	28.9%	<0.0001
Antidepressants (%)	46.4%	59.3%	26.3%	0.002
Hypnotics/benzodiazepines (%)	32.0%	47.5%	7.9%	<0.0001

Because patients taking quadruple-or-more-pharmacotherapy versus up to triple-pharmacotherapy and symptomatic compared with euthymic patients had generally similar aripiprazole dosing patterns, pooled dosing data are presented. Aripiprazole was generally administered in a single daily dose, most often given with dinner, or at bedtime, with an overall mean ± SD (median) final dose of 17.6 ± 10.3 (15) mg/day, after 388 ± 497 (190) days taking aripiprazole at Stanford. In the 80 trials started at Stanford, aripiprazole was initiated at 7.6 ± 4.9 (5) mg/day, increased to at least 15 mg/day in 77.5% (62/80) of patients after 42 ± 74 (12) days, with a maximum dose of 22.0 ± 9.4 (27.5) mg/day, after 75 ± 131 (20) days.

Aripiprazole discontinuation rate and reasons

Aripiprazole was discontinued in only one-quarter (4/16) of euthymic patients taking up to triple-pharmacotherapy (added to up to two other medications), but in two-thirds (55/81, 67.9%, χ^2 = 10.3, df = 1, Fisher's exact test p = 0.002) of other patients (triple-or-more-pharmacotherapy in symptomatic patients and quadruple-or-more-pharmacotherapy in euthymic patients). Thus, aripiprazole was discontinued less often in euthymic patients taking up to triple-pharmacotherapy compared with euthymic patients taking quadruple-or-more-pharmacotherapy (7/12, 58.3%, χ^2 = 3.2, df = 1, Fisher's exact test p = 0.12), symptomatic patients taking up to triple-pharmacotherapy (14/22, 63.6%, χ^2 = 5.5, df = 1, Fisher's exact test p = 0.02), and symptomatic patients taking quadruple-or-more-pharmacotherapy (34/47, 72.3%, χ^2 = 11.2, df = 1, Fisher's exact test p = 0.001) as shown in **Figure 1**. Also, aripiprazole discontinuation rates were higher in all patients taking quadruple-or-more-pharmacotherapy compared with up to triple-pharmacotherapy (69.5%, 41/59 vs. 47.4%, 18/38, χ^2 = 4.7, df = 1, Fisher's exact test p = 0.035), and in all patients who were symptomatic compared with euthymic (69.6%, 48/69 vs. 39.3%, 11/28, χ^2 = 7.7, df = 1, Fisher's exact test p = 0.011).

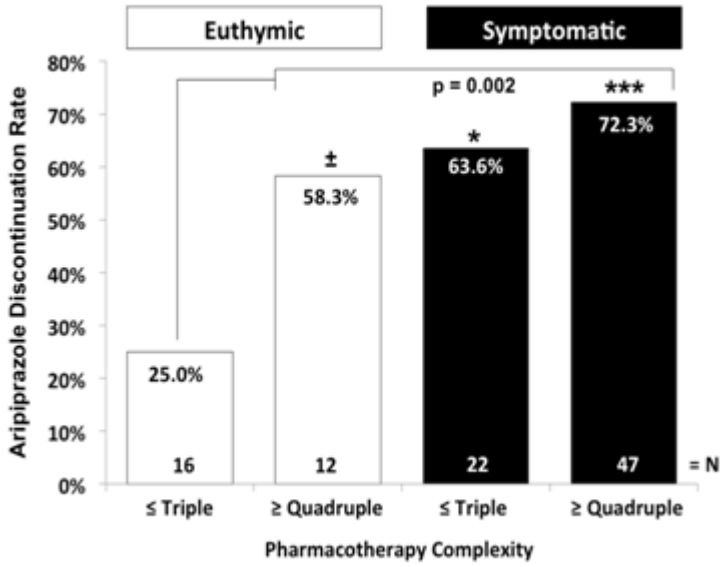

Figure 1. Aripiprazole discontinuation rate increased with pharmacotherapeutic complexity and degree of baseline mood disturbance—from one-quarter in euthymic patients taking up to triple-pharmacotherapy (leftmost bar), to two-thirds in other patients (other 3 bars collectively). Thus, euthymic patients taking up to triple-pharmacotherapy had a lower aripiprazole discontinuation rate compared with all other patients considered collectively (p = 0.002), and to the other individual groups (p = 0.12, *p < 0.05, ***p = 0.001). ≤Triple—indicates patients in whom aripiprazole was added to up to 2 other medications. ≥Quadruple—indicates patients in whom aripiprazole was added to 3 or more other medications.

Patients taking quadruple-or-more-pharmacotherapy compared with up to triple-pharmacotherapy had only nonsignificantly higher rates of discontinuation because of inefficacy for mood (35.6%, 21/59 vs. 26.3%, 10/38, $\chi^2 = 0.92$, df = 1, Fisher's exact test $p = 0.38$), and because of side effects (27.1%, 16/59 vs. 15.8%, $\chi^2 = 1.7$, df = 1, Fisher's exact test $p = 0.22$). Symptomatic compared with euthymic patients had a significantly higher rate of discontinuation because of inefficacy for mood (39.1%, 27/69 vs. 14.3%, 4/28, $\chi^2 = 5.7$, df = 1, Fisher's exact test $p = 0.018$), but only a nonsignificantly higher rate of discontinuation because of side effects (26.1%, 18/69 vs. 14.3%, 4/28, $\chi^2 = 1.6$, df = 1, Fisher's exact test $p = 0.29$). Overall, discontinuations because of inefficacy for mood were most often the result of inefficacy for depression (in 26.8%, 26/97), and only because of inefficacy for mania/hypomania/mixed mood/rapid cycling in 5.2% (5/97), while adverse effect discontinuations were most often because of central nervous system adverse effects (in 17.5%, 17/97), which included discontinuations as a result of akathisia/agitation/anxiety in 6.2% (6/97).

Subsequent additional pharmacotherapy rates and reasons

Patients taking quadruple-or-more-pharmacotherapy compared with up to triple-pharmacotherapy had a nonsignificantly higher rate of subsequent additional pharmacotherapy (59.3 %, 35/39 vs. 47.4%, 18/38, $^2 = 1.3$, df = 1, Fisher's exact test $p = 0.30$), and tended to have a shorter time to subsequent additional pharmacotherapy (102 ± 87 {77} vs. 160 ± 155 {106} days, $t = 1.7$, df = 51, $p = 0.09$. Symptomatic compared with euthymic patients had a higher rate of subsequent additional pharmacotherapy (62.3% vs. 35.7%, $\chi^2 = 5.7$, df = 1, Fisher's exact test $p = 0.024$), and a shorter time to subsequent additional pharmacotherapy (96 ± 81 {77} vs. 233 ± 174 {243} days, $t = –3.8$, df = 51, $p < 0.0001$). Having to add subsequent psychotropic medicine did not predict having to discontinue aripiprazole. Indeed, patients with compared with without subsequent additional pharmacotherapy had a significantly longer mean ± SD (median) duration of aripiprazole therapy (572 ± 571 {429} days vs. 167 ± 253 {74} days) ($U = 390.0$, z = –5.6, $p < 0.0001$).

Because there were similar patterns of reasons for subsequent additional pharmacotherapy for patients taking quadruple-or-more-pharmacotherapy and up to triple-pharmacotherapy and for symptomatic and euthymic patients, pooled data are presented. Depressive symptoms were the most common reason for subsequent additional pharmacotherapy. Thus, subsequent additional pharmacotherapy was administered in 29.9% (29/97) of trials for depressive symptoms, in 12.4% (12/97) for anxiety/insomnia, in 7.2% (7/97) for manic/hypomanic/mixed symptoms, and in 5.2% (5/97) for weight control.

Adverse effects

Because the pattern of adverse effects was similar for patients taking quadruple-or-more-pharmacotherapy and up to triple-pharmacotherapy and for symptomatic and euthymic patients, pooled adverse effect data are presented. Although aripiprazole yielded discontinuations for adverse effects (primarily central nervous system adverse effects, in 22.7% (22/97) of patients, it was otherwise generally well tolerated. Overall, mean ratings for the central nervous system (tremor, sedation, headache, memory problems, akathisia, other extrapyramidal symptoms) and gastrointestinal (nausea, vomiting, diarrhea, constipation) adverse effects, dry mouth, sexual dysfunction and increased appetite were all low at baseline (ranging from 0.00 to 0.84 on a scale with 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe), and did not change significantly at last visit taking aripiprazole (range 0.00 to 0.79).

Discussion

We found aripiprazole in up to triple-pharmacotherapy (added to up to two other medications) may be an effective longer-term treatment for most euthymic bipolar disorder patients. Specifically, aripiprazole was discontinued in only one-quarter of such patients, but in two-thirds of other patients. While registration studies support aripiprazole as a mono-pharmacotherapy or dual-pharmacotherapy (added to lithium or valproate) for acute mania and maintenance treatment [7-10], to our knowledge this is the first study to evaluate the longer-term effectiveness of aripiprazole in triple-or-more-pharmacotherapy of bipolar disorder. Our data suggest that use of aripiprazole in the treatment of bipolar disorder may be modestly extended beyond mono-pharmacotherapy and dual-pharmacotherapy to include up to triple-pharmacotherapy in euthymic patients. However, adding aripiprazole even further beyond the current

indications may not be effective in most other patients (i.e. triple-or-more-pharmacotherapy in symptomatic patients and quadruple-or-more-pharmacotherapy in euthymic patients).

The current United States-based prescribing information recommends doses of 15–30 mg/day for acute bipolar mania and for longer-term treatment recommends continuing the dosage necessary to maintain symptom remission. In our study, the mean final dose was 17.6 mg/day. Additional effectiveness trials are needed to determine whether or not optimal aripiprazole dosing in longer-term bipolar disorder treatment involves using the lower end of the 15–30 mg/day range.

This study has noteworthy strengths and limitations. The sample was derived from a heterogeneous cohort of bipolar disorder patients with diverse clinical presentations, comorbidities, and medication regimens, suggesting more generalizability than might be inferred from controlled trials with restrictive inclusion and exclusion criteria. However, the findings of this study need to be approached with considerable caution in view of noteworthy limitations. Our study failed to decisively demonstrate the extent to which higher discontinuation rates with pharmacotherapeutic complexity and degree of baseline mood disturbance were specific to aripiprazole as distinct from other medications, and related to inefficacy as opposed to tolerability challenges. Our sample was comprised of 80.5% Caucasians, with all patients having medical insurance or being able to afford fee for service, and was derived from a tertiary teaching hospital clinic, also limiting generalizability. For example, the 34.0% lifetime prevalence of comorbid alcohol use disorder in our sample was substantially lower than that reported in national epidemiological studies [22, 23]. An important limitation of our outpatient, more depressed than elevated sample is that the findings may have particularly limited generalizability when considering inpatients with acute manic or mixed episodes or current psychotic symptoms. Another limitation is the possibility that factors other than aripiprazole administration (e.g. prior or subsequent additional medication or nonmedication interventions) could have contributed to the apparent benefits (or lack of benefits) observed with aripiprazole. Other limitations include the relatively small sample size (97 trials), the relatively brief duration (mean 388 days), and the naturalistic open-label design with no placebo or active comparator group.

Nevertheless, our observations support the contention that more research is indicated. Specifically, controlled and additional observational studies appear warranted to confirm these preliminary findings suggesting that use of aripiprazole in the treatment of bipolar disorder may be modestly extended beyond mono-pharmacotherapy and dual-pharmacotherapy to include triple-pharmacotherapy in euthymic patients, but even further extension beyond the current indications may not be effective in most patients.

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References

1. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007; 64:543-52.
2. World Health Organization. The World Health Report 2001 - Mental Health: New Understanding, New Hope. Geneva, Switzerland.: World Helath Organization; 2001.
3. Ketter TA. Handbook of diagnosis and treatment of bipolar disorder. Washington, DC: American Psychiatric Publishing, Inc.; 2010.
4. Ketter TA, Citrome L, Wang PW, Culver JL, Srivastava S. Treatments for bipolar disorder: can number needed to treat/harm help inform clinical decisions?. Acta Psychiatr Scand. 2011; 123:175-89.
5. Frye MA, Ketter TA, Leverich GS, Huggins T, Lantz C, Denicoff KD, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J Clin Psychiatry. 2000; 61:9-15.
6. Goldberg JF, Brooks JO, 3rd, Kurita K, Hoblyn JC, Ghaemi SN, Perlis RH, et al. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. J Clin Psychiatry. 2009; 70:155-62.
7. Young AH, Oren DA, Lowy A, McQuade RD, Marcus RN, Carson WH, et al. Aripiprazole

monotherapy in acute mania: 12-week randomised placebo- and haloperidol-controlled study. Br J Psychiatry. 2009; 194:40-8.
8. Keck PE, Orsulak PJ, Cutler AJ, Sanchez R, Torbeyns A, Marcus RN, et al. Aripiprazole monotherapy in the treatment of acute bipolar I mania: a randomized, double-blind, placebo- and lithium-controlled study. J Affect Disord. 2009; 112:36-49.
9. Keck PE, Jr., Marcus R, Tourkodimitris S, Ali M, Liebeskind A, Saha A, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry. 2003; 160:1651-8.
10. Vieta E, T'Joen C, McQuade RD, Carson WH, Jr, Marcus RN, Sanchez R, et al. Efficacy of adjunctive aripiprazole to either valproate or lithium in bipolar mania patients partially nonresponsive to valproate/lithium monotherapy: a placebo-controlled study. Am J Psychiatry. 2008; 165:1316-25.
11. Keck PE, Calabrese JR, McQuade RD, Carson WH, Carlson BX, Rollin LM, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry. 2006; 67:626-37.
12. Keck PE, Jr, Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study vs. placebo. J Clin Psychiatry. 2007; 68:1480-91.
13. Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. Bipolar Disord. 2011; 13:133-44.
14. Thase ME, Jonas A, Khan A, Bowden CL, Wu X, McQuade RD, et al. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol. 2008; 28:13-20.
15. Quante A, Zeugmann S, Luborzewski A, Schommer N, Langosch J, Born C, et al. Aripiprazole as adjunct to a mood stabilizer and citalopram in bipolar depression: a randomized placebo-controlled pilot study. Hum Psychopharmacol. 2010; 25:126-32.
16. Woo YS, Bahk W-M, Chung MY, Kim D-H, Yoon B-H, Lee JH, et al. Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. Hum Psychopharmacol. 2011; 26:543-53.
17. Ketter TA, Wang PW, Chandler RA, Culver JL, Alarcon AM. Adjunctive aripiprazole in treatment-resistant bipolar depression. Ann Clin Psychiatry. 2006; 18:169-72.
18. Sachs GS, Guille C, McMurrich SL. A clinical monitoring form for mood disorders. Bipolar Disord. 2002; 4:323-7.
19. Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry. 2003; 53:1028-42.
20. Dennehy EB, Bauer MS, Perlis RH, Kogan JN, Sachs GS. Concordance with treatment guidelines for bipolar disorder: data from the systematic treatment enhancement program for bipolar disorder. Psychopharmacol Bull. 2007; 40:72-84.
21. American Psychiatric Association, editor. Diagnostic and statistical manual of mental disorders. Text reision (DSM-IV-TR). 4th ed. Washington: American Psychiatric Association; 2000.
22. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990; 264:2511-8.
23. Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, et al. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2005; 66:1205-15.