Aripiprazole Therapy in 20 Older Adults With Bipolar Disorder: A 12-Week, Open-Label Trial

Martha Sajatovic, M.D.; Nicoleta Coconcea, M.D.; Rosalinda V. Ignacio, M.S.; Frederic C. Blow, Ph.D.; Robert W. Hays, M.A.; Kristin A. Cassidy, M.A.; and William J. Meyer, B.S.

Objective: Bipolar disorder in older adult populations has gained increasing attention due to the growing proportion of elderly in the United States and worldwide. A continuing unmet need is the identification of agents that are generally well-tolerated and effective in later life bipolar disorder. Aripiprazole is an atypical antipsychotic compound that is approved by the U.S. Food and Drug Administration for the treatment of bipolar mania and for the long-term treatment of bipolar disorder. This study is an open-label, prospective trial of aripiprazole therapy in 20 older adult patients with bipolar disorder.

Method: Older adults with bipolar I disorder (confirmed by the Mini-International Neuropsychiatric Interview) who were currently suboptimally responsive to their prescribed medication treatments received 12 weeks of open-label aripiprazole added on to existing mood stabilizer medication treatment. Aripiprazole was initiated at 5 mg daily and increased as tolerated. Efficacy outcomes included psychopathology measures (the Young Mania Rating Scale [YMRS] and the Hamilton Rating Scale for Depression [HAM-D]), extrapyramidal symptoms, and a level of functioning measure (the Global Assessment Scale [GAS]). The study was conducted from April 2004 to June 2005.

Results: Twenty older adults (mean age = 59.6 years, range 50–83 years) received aripiprazole therapy. Compared to baseline, individuals had significant reductions in mean depression scores (HAM-D baseline = 13.8, HAM-D end point = 6.1, $p < .001$), as well as mania scores (YMRS baseline = 8.6, YMRS end point = 3.9, $p < .03$). There were also significant improvements in functional status as measured by the GAS ($p < .001$). The mean ± SD daily dose of aripiprazole was 10.26 ± 4.9 mg/day. Overall, aripiprazole was adequately tolerated in this older adult population.

Conclusion: Aripiprazole therapy may reduce symptoms in bipolar older adults, and it appears to be reasonably tolerated. However, larger, controlled trials are needed to confirm these preliminary findings.

(J Clin Psychiatry 2008;69:41–46)

Received Dec. 6, 2006; accepted April 23, 2007. From the Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, Ohio (Dr. Sajatovic, Ms. Cassidy, and Mr. Meyer); NorthEast Ohio Health Services, Cleveland (Dr. Coconcea and Mr. Hays); and the Serious Mental Illness Treatment Research and Evaluation Center (SMITREC), Health Services Research and Development, Ann Arbor VA Healthcare System and Department of Psychiatry, University of Michigan, Ann Arbor (Dr. Blow and Ms. Ignacio).

This study was supported by Bristol-Myers Squibb.

Data were presented in part at the annual meetings of the American College of Neuropsychopharmacology; Dec. 9–12, 2006; Boca Raton, Fla.; the American Association of Geriatric Psychiatry; March 1–4, 2007; New Orleans, La.; and the American Psychiatric Association; May 19–24, 2007; San Diego, Calif.

Dr. Sajatovic has served as a consultant for AstraZeneca and GlaxoSmithKline; has received grant/research support from Bristol-Myers Squibb and Abbott; has received honoraria from AstraZeneca; and has served on speakers/advisory boards for AstraZeneca and Bristol-Myers Squibb. Dr. Coconcea has served on the speakers board for Bristol-Myers Squibb. Mss. Ignacio and Cassidy, Messrs. Hays and Meyer and Dr. Blow report no additional financial affiliations or other relationships relevant to the subject of this article.

Corresponding author and reprints: Martha Sajatovic, M.D., Department of Psychiatry, University Hospitals of Cleveland, 11100 Euclid Ave., Cleveland, OH 44106 (e-mail: martha.sajatovic@uhhs.com).

The issue of older adults with bipolar disorder has gained increasing attention due to the growing proportion of elderly individuals in the United States and global populations.[1,2] Hirschfeld et al.[3] reported that 1.6% of individuals aged 55 to 64 screen positive for bipolar disorder using a self-completed screening tool, the Mood Disorder Questionnaire, as do 0.5% of individuals age 65 and older. Among older adults, bipolar illness may be first manifested in young adulthood, persisting into later life or, alternatively, may be of more recent onset.[4] Unfortunately, clinicians struggling to meet the needs of geriatric patients with bipolar disorder have few evidence-based studies on which to base treatment decisions, and they often must contend with issues of psychiatric and medical comorbidity in these vulnerable individuals.[5,6] Medications that are noted to be first-line therapies in younger bipolar populations, such as lithium and some of the anticonvulsant compounds,[7,8] are potentially problematic in some elderly individuals due to side effects such as tremor, worsening renal function, or sedation.[5,6] A small but growing literature highlights the complexities of treatment of late-life bipolar disorder,[5,9] and additional treatment strategies for bipolar disorder in older adults are urgently needed.[10,11] Aripiprazole is an atypical antipsy-

chotic compound with partial agonist activity at the dopamine D_2 and 5-HT_{1A} receptors and antagonist activity at the 5-HT_{2A} receptors.[12,13] Aripiprazole is approved by the U.S. Food and Drug Administration for the treatment of bipolar mania and for the long-term treatment of bipolar disorder. Centorrino et al.[14] recently noted the apparently benign adverse-effect profile of aripiprazole, including limited weight gain, in a population of 142 adult inpatients treated for a variety of disorders. Relatively low risk of weight gain and metabolic concerns may be a particularly attractive aspect of this compound for older populations, which are predisposed to obesity and diabetes. This article is a first report of a prospective trial of adjunctive aripiprazole therapy among 20 older adults with bipolar disorder.

METHOD

This study was an open-label, 12-week prospective trial of add-on aripiprazole therapy in 20 older adults (aged 50 and older) with bipolar type I disorder as confirmed by the Mini-International Neuropsychiatric Interview (M.I.N.I.).[15] The study was conducted from April 2004 to June 2005 in the ambulatory care setting of University Hospitals of Cleveland in Ohio. It focused on older adults with bipolar disorder who were currently receiving medication treatment for their symptoms but who continued to experience either residual symptoms of their illness or were experiencing burdensome side effects from currently prescribed psychotropic compounds. This type of older adult with bipolar illness is common in typical clinical practice settings and may be conceptualized as having suboptimal response to bipolar medication treatments. Individuals were defined as suboptimally responsive to current psychotropic treatments and eligible to participate if, based on either self-report or report of care providers, they had (1) behaviors and symptoms of irritability, agitation, mood lability, or diminished ability to interact with others in their place of residence (N = 9, 45% of patients enrolled); (2) diminished ability to take care of basic personal needs in their place of residence due to symptoms of bipolar disorder (N = 2, 10% of patients enrolled); or (3) intolerance to current psychotropic medications (N = 9, 45% of patients enrolled). Some individuals (N = 6, 30% of patients enrolled) fit more than 1 of the suboptimal response criteria. A single rater, trained to study protocol procedures, screened for suboptimal response entry criteria with clinical assessment concurrence by the study principal investigator (M.S.). All patients provided written informed consent, and the study protocol was approved by the local institutional review board. Individuals with acute medical illness and those with a clinical diagnosis of dementia were excluded from study participation.

Patients were continued on treatment with their existing mood-stabilizing medication and, upon enrollment, were initiated on aripiprazole augmentation treatment.

Table 1. Clinical Characteristics of 20 Older Adults With Bipolar Disorder Receiving Adjunctive Aripiprazole Therapy

Variable	Value
Sex, N (%)	
Male	6 (30)
Female	14 (70)
Age, mean ± SD (range), y	59.55 ± 8.5 (50–83)
Ethnicity, N (%)	
White	16 (80)
African American	4 (20)
Traditional mood stabilizer treatment, N (%)	
Lithium	3 (15)
Valproate	3 (15)
Lamotrigine	8 (40)
Most common comorbid medical conditions, N (%)	
Hypertension	11 (55)
Arthritis	9 (45)
Coronary artery disease	7 (35)
Diabetes	3 (15)
Hyperlipidemia	3 (15)
Asthma	3 (15)
Chronic pain/fibromyalgia	3 (15)
Migraine	3 (15)
Dose of aripiprazole at end of study, mean ± SD (range), mg/d	10.26 ± 4.9 (5–20)

The initial starting dose of aripiprazole was 5 mg/day, with gradual upward titration as tolerated. Initiation of new antipsychotic medications was not permitted during the course of the study, and antipsychotic medications prescribed at study start were tapered and discontinued by week 4 of the study if possible. Measured symptom and psychopathology outcomes included the Young Mania Rating Scale (YMRS)[16] and the Hamilton Rating Scale for Depression (HAM-D).[17] Extrapyramidal symptoms were evaluated with the Abnormal Involuntary Movement Scale,[18] the Barnes Akathisia Scale,[19] and the Simpson-Angus Scale.[20] Level of functioning was assessed with the Global Assessment Scale (GAS).[18] All rating scale measures were conducted at baseline and at the conclusion of weeks 1, 2, 4, 8, and 12 (end of study). Patients had baseline assessment of basic serum chemistry, metabolic profile, complete blood count with differential, vital signs, weight, and electrocardiogram (ECG) at baseline. Vital signs and weight were assessed at each study visit, and laboratory testing and ECG were repeated at end of study.

Efficacy and safety results were calculated using descriptive statistics. Scores for each rating scale over time were evaluated using paired t test comparing baseline and last available assessment of each measure. The intent-to-treat (ITT) population was defined as individuals who received at least 1 dose of aripiprazole.

RESULTS

Clinical Characteristics of the Sample

Table 1 illustrates the clinical characteristics of the sample at baseline. Mean ± SD age was 59.6 ± 8.5 years,

Table 2. Psychopathology, Functional Status and Extrapyramidal Rating Scale Scores Among 20 Older Adults With Bipolar Disorder Receiving 12 Weeks of Adjunctive Aripiprazole Therapy[a]

	Measure					
Time in Study	YMRS	HAM-D	GAS	AIMS	SAS	BAS
Baseline	8.63 ± 5.66*	13.78 ± 6.64**	57.58 ± 5.98**	0.94 ± 2.41	0.39 ± 1.42	0.44 ± 1.04
Week 1	8.71 ± 4.50	8.82 ± 3.97	63.65 ± 6.86	0.29 ± 1.21	0.18 ± 0.53	0.24 ± 0.75
Week 2	8.44 ± 4.90	6.50 ± 4.76	67.83 ± 10.38	0.39 ± 0.98	0.06 ± 0.24	0.56 ± 1.29
Week 4	6.31 ± 3.61	7.19 ± 4.75	71.13 ± 11.37	0.47 ± 1.06	0.38 ± 0.62	0.62 ± 1.36
Week 8	4.40 ± 3.50	8.33 ± 6.88	72.93 ± 12.42	0.33 ± 1.29	0.20 ± 0.77	0.13 ± 0.52
Week 12	3.94 ± 2.05	6.06 ± 3.71	77.19 ± 10.61	0.19 ± 0.75	0.38 ± 0.81	0.31 ± 1.25

[a]Values are shown as mean ± SD.
*$p < .05$ for paired t test: change from baseline vs. last observed value.
**$p < .01$ for paired t test: change from baseline vs. last observed value.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Akathisia Scale, GAS = Global Assessment Scale, HAM-D = 17-item Hamilton Rating Scale for Depression, SAS = Simpson-Angus Scale, YMRS = Young Mania Rating Scale.

range 50–83 years, and most individuals were female (N = 14, 70%) and white (N = 16, 80%). At baseline, the majority of these older bipolar patients had moderate-to-mild depressive symptoms (mean ± SD HAM-D score = 13.8 ± 6.6, range 1–30). There were 2 individuals with mania at baseline (subject with mania, YMRS score = 21 and subject with mixed mania, YMRS score = 22). Psychotic symptoms were present in 1 individual (5%) as identified on the M.I.N.I.

Most individuals (N = 13, 65%) were maintained on traditional mood stabilizing medications at baseline, including lithium (N = 3, 15%), divalproex (N = 3, 15%), and lamotrigine (N = 8, 40%). There were 8 individuals (40%) who were maintained on antidepressant medications. There were 8 individuals who were receiving antipsychotic medication at study initiation. Antipsychotic medications were tapered and discontinued during the first 4 weeks of the study. However, 5 individuals could not be entirely tapered off antipsychotic medication. Among this group, 4 individuals would not agree to discontinuation of low-dose quetiapine (25–100 mg/day) for management of insomnia, and 1 individual with a history of very severe depression/suicidality remained on low-dose olanzapine (5 mg/day), as it appeared to have benefited him in the past, and it was felt that discontinuation of the olanzapine might lead to clinical worsening. Three patients (15%) were receiving maintenance benzodiazepines, 2 individuals were receiving benztropine, and 1 individual (with bipolar depression) was receiving a maintenance stimulant compound for treatment of comorbid adult attention-deficit/hyperactivity disorder.

Comorbid medical conditions were common and included hypertension (N = 11, 55%), arthritis (N = 9, 45%), coronary artery disease (N = 7, 35%), diabetes (N = 3, 15%), hyperlipidemia (N = 3, 15%), asthma (N = 3, 15%), chronic pain/fibromyalgia (N = 3, 15%), migraine (N = 3, 15%), hypothyroidism (N = 2, 10%), gastroesophageal reflux disease/irritable bowel syndrome (N = 2, 10%), and psoriasis (N = 1, 5%).

Efficacy

Table 2 illustrates psychopathology, functional status, and extrapyramidal ratings scores at all study assessment points. HAM-D improvement was substantial and significant ($p = .0004$), while YMRS scores improved significantly ($p = .0267$) but only modestly. The 2 patients with mania had significant clinical improvement (YMRS score = 21 at baseline and YMRS score = 2 at end point for 1 individual, and YMRS score = 22 at baseline and 4 at end point for a second individual). One patient had been receiving outpatient electroconvulsive therapy (ECT) on a monthly basis for treatment of recurrent depressive symptoms just prior to enrollment, and this individual was able to discontinue maintenance ECT within 4 weeks after beginning aripiprazole therapy. There were also significant improvements in functional status as measured by the GAS ($p < .001$).

There was no significant difference in treatment response based on change from baseline on YMRS, HAM-D, and GAS scores comparing individuals who were identified as intolerant to prescribed psychotropic medications prior to entering study versus individuals who did not have intolerance to medication prior to entering study ($p > .05$). While study entry criteria for suboptimal response were not reassessed at study end point, 16/20 individuals (all those who completed the study on aripiprazole) elected to continue study medication after the study was concluded.

Tolerability

Aripiprazole was fairly well tolerated in this older adult bipolar population. Four patients prematurely discontinued study medication; however, no patients discontinued prematurely due to adverse events. Reasons for premature study discontinuation included lack of efficacy in 2 patients (10%) and nonadherence with medication in 2 patients (10%). One patient in this outpatient study was nonadherent to study protocol and procedures prior to taking a single dose of aripiprazole and thus is not included in the ITT dataset. The majority of patients

(N = 12, 63%) did not experience adverse effects on aripiprazole therapy.

As might be expected, there was a trend for greater medical comorbidity among individuals who experienced adverse effects (mean ± SD number of comorbid medical conditions in adverse effect group = 3.0 ± 1.8 vs. mean ± SD number of comorbid medical conditions in nonadverse effects group = 1.9 ± 1.1), p = .075, t = 1.5, df = 11.

Adverse effects experienced by this group of older bipolar patients included restlessness (N = 3, 15.8%), weight gain over 7% of baseline (N = 3, 15.8%), sedation (N = 2, 10.5%), insomnia (N = 1, 5.3%), drooling (N = 1, 5.3%), and diarrhea/loose stools (N = 1, 5.3%). Mean ± SD body weight was 86.3 ± 20.10 kg at baseline and 88.6 ± 18.09 kg at end point, with mean ± SD weight gain of 1.4 ± 3.86 kg after 12 weeks (p = .1292). Extrapyramidal symptom ratings were not significantly different from baseline to end point (p > .05). Mean ± SD daily dose of aripiprazole was 10.26 ± 4.9 mg/day, range 5–20 mg/day. Mean ± SD baseline and end point serum glucose (nonfasting) levels were 95.6 ± 15.8 mg/dL and 86.4 ± 10.2 mg/dL, respectively (p = .031); mean ± SD baseline and end point serum triglyceride levels (nonfasting) were 155.5 ± 103.0 mg/dL and 153.5 ± 92.2 mg/dL, respectively (p = .916); mean baseline and end point serum low-density lipoprotein levels were 119.2 ± 28.4 mg/dL and 106.6 ± 31.7 mg/dL, respectively (p = .242); and mean ± SD baseline and end point serum high-density lipoprotein levels were 58.8 ± 21.5 mg/dL and 57.1 ± 19.0 mg/dL, respectively (p = .490). There were no clinically significant changes in vital signs, laboratory testing, or ECG.

DISCUSSION

This open-label, pilot study of adjunctive aripiprazole therapy suggests that aripiprazole may reduce symptoms in bipolar older adults, and it appears to be adequately tolerated. The majority of older bipolar patients in this study were experiencing moderate/mild depressive symptoms at baseline, and there was an overall significantly positive improvement in depressive symptoms.

There are few prospective studies of geriatric bipolar disorder,[9] and to the best of our knowledge, no published randomized, controlled trials. Findings from retrospective analyses and case reports suggest that the atypical antipsychotics olanzapine,[21] risperidone,[22,23] quetiapine,[24] and clozapine[25] may be of benefit in the treatment of geriatric bipolar patients. Our findings suggest that aripiprazole may also be efficacious and well-tolerated in later life bipolar disorder, particularly among individuals with bipolar depression.

The challenge of managing bipolar depression has been highlighted by a number of publications.[26–28] Unfortunately, the majority of individuals with bipolar disorder experience substantial intervals of depressed mood, with coexistent decline in functioning and quality of life.[27,29] Depp et al.[30] recently evaluated health-related quality of life among middle-aged and older adults with bipolar disorder and noted that depressive symptoms, along with psychosis and cognitive impairment, significantly contribute to reduced quality of life. There are a limited number of agents known to be efficacious for the treatment of bipolar depression, and use of antidepressant compounds is potentially problematic due to possible precipitation of mania or rapid cycling.[7] Among older adults, the addition of multiple psychotropic agents to stabilize mood and treat depressive symptoms may be a greater concern due to the risks of polypharmacy in the elderly.[31,32]

Recently, Simon and Nemeroff[33] demonstrated that use of aripiprazole is an effective augmentation strategy for improving therapeutic response in patients with treatment-refractory unipolar depression. This finding is consistent with other reports noting the effects of improvement in depressive symptoms and global functioning with the addition of an atypical antipsychotic compound to the treatment regimen of patients with depression.[34–36] Aripiprazole is a partial agonist of the dopamine D_2 and serotonin 5-HT_{1A} receptors and an antagonist of the serotonin 5-HT_{2A} receptor.[12,13] It has been speculated that partial 5-HT_{1A} receptor agonism may be associated with antidepressant effects.[12,33,37] Among individuals with bipolar depression, the atypical antipsychotics quetiapine and olanzapine have both been demonstrated to have antidepressant effects.[38,39]

Aripiprazole was adequately tolerated in this older adult population, with the primary side effects being restlessness and weight gain (15.8% for each) and sedation (10.5%). Mean weight increase was approximately 1.4 kg. The older adult bipolar sample in this study had substantial medical comorbidity consistent with reports in geriatric bipolar populations noted by other investigators.[30] Depp et al.[30] demonstrated that bipolar older adults (mean age = 57.6 years) have significantly more medical comorbidity compared to similarly aged individuals with schizophrenia (mean age = 58.5 years) and individuals with no psychiatric illness (mean age = 64.7 years). In the study reported here, there was a trend for individuals with greater baseline medical comorbidity to experience more adverse effects with aripiprazole therapy. While recent publications have highlighted potential risks of use of atypical and typical antipsychotics in elderly patients, primarily among individuals with dementia,[40–42] there are conflicting reports regarding the risk of antipsychotic medication treatment in populations with serious mental illness. Enger et al.[43] noted that, among patients with schizophrenia, cardiovascular risk is inversely associated with intensity of use of antipsychotic drugs and that risk of myocardial infarct is reduced with increased exposure to antipsychotic medication treatments. Larger, controlled

trials are needed to more fully understand the potential risks and benefits of the scope of available treatments for bipolar disorder among geriatric populations.

The findings of this study must be interpreted cautiously, given the limitations of small sample size, open-label, add-on design, and lack of a control group or placebo arm. The continuation of previously prescribed bipolar medication treatments may have contributed to improvement in symptoms. An additional limitation is that no minimum symptom rating scale criteria were used for sample selection. Baseline symptom scores were on average low for mania and mild to moderate for depression, and these scores limit ability to detect efficacy for reduction in symptoms and subsequent interpretation of results. Finally, the sample mean age of approximately 60 years is not representative of the "old-old" populations seen in some geriatric-focused studies, and results cannot necessarily be extrapolated to the oldest geriatric bipolar populations.

CONCLUSION

This uncontrolled prospective study of aripiprazole therapy in older adults suggests that individuals who are suboptimally responsive to traditional mood stabilizing medication may benefit from adjunctive aripiprazole. Aripiprazole was adequately tolerated in this older population with substantial medical comorbidity. Older adults with bipolar depression appeared to have significant improvements in depressive symptoms, a finding of particular interest given the typical difficulty in treating bipolar depression and the effects of residual depressive symptoms on health-related quality of life.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (Fazaclo, Clozaril, and others), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), quetiapine (Seroquel), valproate (Depakote and others).

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Trends in aging—United States and worldwide. MMWR Morb Mortal Wkly Rep 2003; 52:101–104, 106
2. Jeste DV, Alexopoulos S, Bartels S, et al. Consensus statement on the upcoming crisis in geriatric mental health. Arch Gen Psychiatry 1999; 56:848–853
3. Hirschfeld RM, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;64:53–59
4. Chen P, Ahmed M, Sajatovic M. Bipolar disorder in later life. J Aging Health. In press
5. Depp CA, Jeste DV. Bipolar disorder in older adults: a critical review. Bipolar Disord 2004;6:343–367
6. Young RC, Gyulai L, Mulsant BH, et al. Pharmacotherapy of bipolar disorder in old age: review and recommendations. Am J Geriatr Psychiatry 2004;12:342–357
7. American Psychiatric Association. Practice Guideline for the Treatment of Patients with Bipolar Disorder (Revision). Am J Psychiatry 2002;159 (suppl 4):1–50
8. Keck PE, Perlis RH, Otto MW, et al. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder 2004. Postgrad Med Special Report Dec 2004:1–120
9. Gildengers AG, Mulsant BH, Begley AE, et al. A pilot study of standardized treatment in geriatric bipolar disorder. Am J Geriatr Psychiatry 2005;13:319–323
10. Young RC. Randomized, controlled trial of lithium vs valproate in geriatric mania. Presented at the 6th International Congress on Bipolar Disorder; June 16–18, 2005; Pittsburgh, Pa
11. Geddes J, Goodwin G, Rendell J, et al. New trial should clarify lithium use in bipolar disorder. BMJ 2002;325:441
12. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. Eur J Pharmacol 2002;441:137–140
13. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 2004;18:251–267
14. Centorrino F, Fogarty KV, Cimbolli P, et al. Aripiprazole: initial clinical experience with 142 hospitalized psychiatric patients. J Psychiatr Pract 2005;11:241–247
15. Sheehan DV, Lecubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): development and validation of a Structured Diagnosis Psychiatric Interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
16. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–435
17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatr 1960;23:56–62
18. Guy W. ECDEU Assessment Manual for Psychopharmacology, rev ed. US Department Health, Education, and Welfare Publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
19. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
20. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
21. Beyer JL, Siegal A, Kennedy JS, et al. Olanzapine, divalproex and placebo treatment, non–head to head comparisons of older adult acute mania. Presented at the 53rd Institute on Psychiatric Services; October 10–14, 2001; Orlando, Fla
22. Madhusoodanan S, Brenner R, Araujo L, et al. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995;56:514–518
23. Madhusoodanan S, Suresh P, Brenner R, et al. Experience with the atypical antipsychotics—risperidone and olanzapine in the elderly. Ann Clin Psychiatry 1999;11:113–118
24. Sajatovic M, Calabrese J, Mullen. Quetiapine for the treatment of bipolar mania in older adults. Presented at the 6th International Congress on Bipolar Disorder; June 16–18, 2005; Pittsburgh, Pa
25. Schulman RW, Singh A, Shulman KI. Treatment of elderly institutionalized bipolar patients with clozapine. Psychopharmacol Bull 1997;33: 113–118
26. Grunze H. Reevaluating therapies for bipolar depression. J Clin Psychiatry 2005;66(suppl 5):17–25
27. 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;59:530–537
28. Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. Am J Psychiatry 2006;163:210–216
29. Altshuler LL, Gitlin MJ, Mintz J, et al. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J Clin Psychiatry 2002;63:807–811
30. Depp CA, Davis CE, Mittal D, et el. Health-related quality of life and functioning of middle-aged and elderly adults with bipolar disorder. J Clin Psychiatry 2006;67:215–221
31. Fuller M, Sajatovic M. Drug Information Handbook for Psychiatry, 3rd ed. Cleveland, Ohio: Lexi-Comp Inc; 2002
32. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord 2005;7 (suppl 3):5–69
33. Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressants

for the treatment of partially responding and nonresponding patients with major depressive disorder. J Clin Psychiatry 2005;66:1216–1220
34. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry 1999;60: 256–259
35. Papakostas GI, Petersen TJ, Nierenberg AA, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. J Clin Psychiatry 2004;65:217–221
36. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158: 131–134
37. Rausch JL, Ruegg R, Moeller FG. Gepirone as a 5-HT 1A agonist in the treatment of major depression. Psychopharmacol Bull 1990;26:169–173
38. 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;162:1351–1360
39. Tohen MF, Ketter TA, Calabrese JR, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079–1088
40. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medications. N Engl J Med 2005;353:2335–2341
41. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943
42. U.S. Food and Drug Administration Center for Drug Evaluation and Research Public Health Advisory, Deaths with antipsychotics in elderly patients with behavioral disturbances. April 11, 2005
43. Enger C, Weatherby L, Reynolds RF, et al. Serious cardiovascular events and mortality among patients with schizophrenia. J Nerv Ment Dis 2004; 192:19–27