Adv Ther (2009) 26(6):588-599.
DOI 10.1007/s12325-009-0039-0

REVIEW

Long-Acting Risperidone: a Review of its Role in the Treatment of Bipolar Disorder

David E. Kemp · Fatih Canan · Benjamin I. Goldstein · Roger S. McIntyre

Received: February 3, 2009 / Published online: June 30, 2009 / Printed: July 10, 2009

ABSTRACT

Bipolar disorder is a multidimensional illness typified by fluctuating periods of depression and mania, cognitive dysfunction, abnormal circadian rhythms, and multiple comorbid psychiatric and general medical conditions. Indefinite pharmacological treatment is often required, yet the modest effects of available treatments and frequent difficulties with tolerability and adherence present complex challenges to patients. Long-acting injectable medications offer a therapeutic alternative to oral mood stabilizers and may help facilitate long-term treatment adherence. This article will provide a succinct review of the latest data on the use of long-acting injectable risperidone (LAR) during the maintenance-phase treatment of bipolar disorder. The specific role of LAR in comparison to other atypical antipsychotics, and the limitations of available studies will be discussed from the perspectives of efficacy, tolerability, and sequential positioning in treatment guidelines.

Keywords: adherence; bipolar disorder; long-acting risperidone; maintenance phase; risperidone

David E. Kemp (✉)
Mood & Metabolic Clinic, Case Western Reserve University, University Hospitals Case Medical Center, 10524 Euclid Avenue, 12th Floor, Cleveland, OH 44106, USA. Email: kemp.david@gmail.com

Fatih Canan
Duzce University Medical School, Duzce, Turkey

Benjamin I. Goldstein
Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Roger S. McIntyre
Mood Disorders Psychopharmacology Unit, University Health Network, Associate Professor of Psychiatry and Pharmacology, University of Toronto, Toronto, USA

INTRODUCTION

Bipolar disorder is an impairing, life-long illness characterized by recurrent episodes of depression and mania.[1] The population prevalence of bipolar disorder has been estimated at approximately 4%,[2] translating into almost 12 million individuals affected by the illness in the US alone. Recognized as the sixth leading cause of disability worldwide,[3] bipolar disorder not only results in disability and functional impairment,[4] but is also associated with an

Springer Healthcare Communications

increase in all-cause and premature mortality.[5,6] Individuals with bipolar disorder experience a shortened life expectancy both from suicide and natural causes of death, including cardiovascular and respiratory diseases.[5-7]

Although first-line treatments for bipolar disorder have traditionally comprised lithium and anticonvulsants, an evidence base is rapidly expanding to include medications of the atypical antipsychotic class as efficacious treatment options.[8-10] Many such pharmacotherapies are effective for the acute treatment of bipolar mania, but insufficient data exist on the longer-term or maintenance treatment of bipolar disorder. Maintenance-phase studies are typically conducted over 6 months to 2 years, and evaluate both recurrence rates and the time to recurrence as primary outcomes. During this period, patient adherence to a medication regimen is paramount to sustaining successful outcomes. However, up to half of patients with bipolar disorder are nonadherent or only partially adherent to antipsychotic treatment.[11] For this reason, novel delivery systems that may improve adherence deserve careful consideration in the pragmatic management of bipolar disorder. The arrival of long-acting injectable risperidone (LAR), originally approved for the treatment of schizophrenia, may be ideally suited for the maintenance phase treatment of bipolar disorder and deserves careful scrutiny through naturalistic reports and randomized, controlled trials.

This manuscript will discuss the available evidence on the use of LAR in bipolar disorder. Efficacy in relieving acute mood symptoms and in preventing the recurrence of new mood episodes will be reviewed. Additionally, the role of maintenance antipsychotic medications in general, and long-acting injectable treatments in particular, will be evaluated from the perspectives of efficacy, tolerability, and positioning within treatment guidelines.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

LAR achieves its therapeutic action through antagonism at the serotonin 5-HT_{2A} and dopamine D_2 receptors (Table 1).[12] It also acts as a moderate antagonist at histaminergic H_1 and adrenergic alpha-1 and alpha-2 receptors, but has little or no affinity for cholinergic muscarinic or beta-1 and beta-2 adrenergic receptors. The long-acting formulation demonstrates linear pharmacokinetics within the 25-75 mg dose range. Intramuscular (i.m.) and oral preparations are bioequivalent, but in contradistinction to the oral formulation, LAR is associated with lower steady-state peak concentrations and less fluctuation in plasma levels.[13] The absence of first-pass hepatic metabolism and the slow, predictable hydrolysis of risperidone microspheres could result in a lower absolute dose of the long-acting formulation being as efficacious as higher oral doses.[13] The elimination half-life of the active metabolite, 9-hydroxyrisperidone, is 3-6 days. Initially, there is only a small release of drug (<1% of total dose); 3 weeks later, significant release begins and is maintained for 4-6 weeks.[15] Therefore, oral risperidone will need to be supplemented during the first 3 weeks of treatment with LAR.

The metabolism of risperidone occurs primarily through the liver. The major pathway involves hydroxylation of risperidone to 9-hydroxyrisperidone by the cytochrome CYP 2D6 isoenzyme; a minor pathway occurs through N-dealkylation.[15] Risperidone is a relatively weak inhibitor of CYP 2D6, and thus is not expected to substantially inhibit the clearance of drugs that are metabolized by this metabolic pathway. Coadministration of

Table 1. Properties of long-acting risperidone (LAR).

Pharmacodynamics[12]	Serotonin 5-HT_{2A}, dopamine D_2, histaminergic H_1, and adrenergic alpha-1 and alpha-2 antagonist
	Increasing degrees of D_2-receptor occupation with increasing doses of LAR injection
	Little or no affinity for cholinergic muscarinic or beta-1 and beta-2 adrenergic receptors.
Pharmacokinetics[13]	Repeated administration every 2 weeks achieves steady-state plasma levels after the fourth injection
	Linear pharmacokinetics
	Intramuscular and oral preparations are bioequivalent but LAR is associated with lower steady-state peak concentrations and fewer fluctuations in plasma levels compared with oral treatment.
Metabolism and elimination[14]	Metabolized by cytochrome P-450 (CYP) isoenzyme 2D6 to 9-hydroxyrisperidone
	Half-life of LAR is 3-6 days because of the extended-release profile rather than the metabolic half-life (N-dealkylation is an alternative pathway)
	LAR is completely eliminated from the body after 6-7 weeks.

carbamazepine or other known enzyme inducers may result in decreased plasma concentrations of risperidone or its active metabolite. Conversely, coadministration with inhibitors of 2D6 will shift the balance away from production of the active metabolite,[15] potentially increasing extrapyramidal symptoms (EPS) or other side effects.

DOSING

For patients naïve to risperidone, it is recommended that tolerability first be established with the oral formulation. Once tolerability is confirmed, LAR should be administered every 2 weeks as either a deltoid or gluteal injection. The recommended dose is 25 mg i.m. every 2 weeks for all adults, including elderly patients.[15] For those patients who do not respond to the 25 mg dose, additional benefit may occur with either the 37.5 or 50 mg i.m. dose. Increases in dose should not be made more frequently than every 4 weeks. For those patients with hepatic or renal impairment, a lower initial dose of 12.5 mg i.m. may be appropriate, although this dose strength has not been evaluated in clinical trials.[15]

EFFICACY STUDIES

Oral Risperidone

Oral risperidone has been rigorously evaluated in the treatment of acute manic or mixed episodes associated with bipolar I disorder.[16,17] Compared with placebo, risperidone demonstrates a clear advantage in the treatment of mania, as evidenced by greater rates of response (≥50% improvement in mania symptom severity) and larger reductions in Young Mania Rating Scale (YMRS) total scores.[18] In addition, risperidone plus a mood stabilizer has been shown to be more efficacious than a mood stabilizer alone for the rapid control of manic symptoms.[19,20] Although risperidone is generally well tolerated, EPS may develop, with some studies reporting EPS rates up to fivefold greater than placebo.[21] Despite established efficacy and US Food and Drug Administration (FDA) approval for the treatment of acute bipolar mania, oral risperidone has not been systematically studied for the prevention of relapse or recurrence during the maintenance phase. Additionally, studies of mania have predominantly evaluated the

antimanic efficacy of risperidone as monotherapy, with fewer trials adjunctive to conventional mood stabilizers.

Preliminary Findings with LAR

Preliminary data on the use of LAR in bipolar disorder were made available by several investigator-initiated trials or observational reports. Although these studies are limited by small sample sizes, they evaluated patients over several months and/or years of observation. In contrast, studies of oral risperidone often lasted a maximum of 3 weeks, consistent with trials of acute mania. A summary of open-label and double-blind studies of LAR is provided in Table 2.[22-28]

Savas and colleagues[22] provided descriptive outcomes on 12 acutely manic or hypomanic patients with bipolar I disorder who were either switched to or received adjunctive LAR due to noncompliance. During a 6-month treatment period, all 12 patients experienced at least ≥50% improvement on the Bech-Rafaelsen Mania Rating Scale (BRMAS), while 11 patients achieved remission (BRMAS score ≤9). LAR was well tolerated; the most frequently reported adverse events were constipation and dizziness reported by 8% and 16% of patients, respectively.

Han and colleagues[23] evaluated LAR over a 12-month period in 10 stable bipolar I patients who were switched from their existing oral antipsychotic agents. No relapses occurred during the study period, and Clinical Global Impression of Severity (CGI-S) scores significantly decreased from a baseline of 3.10±0.57 to a post-12-month treatment score of 1.70±0.48 (P<0.01). No participants reported any serious adverse events during the study period.

Similar outcomes with LAR (25-50 mg every 2 weeks) were reported by Malempati and colleagues[24] who enrolled patients (n=10) with bipolar I and II disorder over a longer observation period (2 years). The authors reported that adjunctive LAR obviated the need for any patient to be hospitalized for a mood episode. In contrast, during the 2 years prior to initiating LAR, patients required an average of 1.6 hospitalizations. Moreover, the average number of medications prescribed per patient decreased from six to three over the observation period. Unlike prior reports that had enrolled patients with an index episode of mania, this study enrolled individuals whose index episode at entry was predominantly depression.

Vieta and colleagues[25] also reported 2-year outcomes in 29 patients receiving LAR for bipolar I disorder. During the follow-up period, there was a significant decrease in the number of hospitalizations per patient (P<0.006), the number of manic or mixed episodes leading to hospitalization (P<0.007), and the average length of hospitalization per patient (P<0.001). A significant increase also occurred in the time to developing any new mood episode (P<0.001) and in the rates of treatment adherence (P<0.0001). However, no significant difference was found in the number of suicide attempts or the number of hospitalizations due to depressive episodes.

Whereas the aforementioned studies of LAR employed naturalistic or nonrandomized study methods, Yatham and colleagues were the first to employ a randomized design.[26] In their 6-month study, 49 patients with bipolar I or II disorder who were taking a mood stabilizer and an atypical antipsychotic were randomized to continue taking the antipsychotic (n=26) or were switched to LAR (n=23). Participants in the LAR group experienced significant reductions from baseline in CGI-S scores and YMRS scores at the endpoint, whereas patients receiving oral atypical antipsychotics (eg, risperidone, quetiapine, or olanzapine) experienced reductions in Hamilton Anxiety Rating Scale (HAM-A) scores relative to baseline. Despite the beneficial within-group changes,

Table 2. Characteristics of clinical trials of long-acting risperidone (LAR) in bipolar disorder.

Study	Methodology	Duration (weeks)	Bipolar subtype (BP)	Monotherapy	Dose (mg per 2 weeks)	Index episode	Outcome
Savas et al. (2006)[22]	Open-label Chart review Acute	24	BP I (n=12)	No	25-50	Not defined	100% response 92% remission Significant decrease in BRMAS No significant change in HAMD
Han et al. (2007)[23]	Open-label Observational Relapse prevention	52	BP I (n=10)	No	25-37.5	Mania/mixed	No significant change in YMRS No significant change in HAMD No relapses occurred
Malempati et al. (2008)[24]	Open-label Observational Relapse prevention	104	BP I (n=8) BP II (n=2)	No	25-50	Not defined	50% relapse
Vieta et al. (2008)[25]	Open-label Observational Acute and relapse prevention	104	BP I (n=29)	No	25-50	Mania	Time to relapse increased Significant decrease in hospitalizations for mania and mixed episodes No decrease in hospitalizations for depression
Yatham et al. (2007)[26]	Open-label Randomized Relapse prevention	24	BP I (n=32) BP II (n=17)	No	25-50	Not defined	Significant reduction in YMRS scores (No difference from OAA group) No change in MADRS scores (No difference from OAA group)
Kujawa et al. (2008)[27]	Double-blind Randomized Relapse prevention	52	BP I (n=124) BP II (n=15)	No	25-50	Mania/mixed (n=80) Hypomania (n=14) Depression (n=45)	Efficacy outcomes expected to be released in late 2009 or early 2010
Johnson & Johnson (2008)[28]	Double-blind Randomized Relapse prevention	104	BP I (n=303)	Yes	12.5-50	Mania/mixed	Efficacy outcomes expected to be released in late 2009 or early 2010

BRMAS=Bech-Rafaelson Mania Rating Scale; HAMD=Hamilton Depression Rating Scale; LAR=long-acting risperidone; MADRS=Montgomery-Asberg Depression Rating Scale; OAA=oral atypical antipsychotic; YMRS=Young Mania Rating Scale.

there were no significant between-group differences on any of the efficacy measures. Likewise, there were no significant differences between groups in adverse events, body weight, change in EPS, or other safety measures, except for a significant reduction in diastolic blood pressure (–5.2±11 mmHg) in the LAR group ($P<0.05$). A power analysis based on the change in YMRS scores between the two groups revealed an effect size of 0.30. In order to detect a significant difference at $P<0.05$ with 80% power for this effect size, a sample size of over 170 patients would have been required. The authors concluded that such marginal reductions in mania symptoms would likely not represent a clinically meaningful improvement.

Large-Scale Studies of LAR

Two adequately powered studies of LAR in the treatment of bipolar disorder were designed and conducted primarily for regulatory approval. These two studies enrolled a total of 834 participants and were conducted over 12 and 24-months duration, respectively.[27,28] Although the results of both studies have been presented at scientific fora, neither trial had been published at the time of preparing this review.

The 12-month trial examined the efficacy of LAR for the prevention of mood relapse when added to an existing psychotropic drug regimen.[27] The trial design consisted of an initial 16-week open-label treatment phase, followed by a 52-week randomized, double-blind, relapse-prevention phase. Enrollment was limited to patients 18-70 years of age with frequently relapsing bipolar I or II disorder (FRBD). FRBD was defined as the occurrence of four of more mood episodes requiring clinical intervention during the past year, with at least two episodes occurring within the previous 6 months. During the 16-week stabilization phase, 275 patients received LAR injection 25, 37.5, or 50 mg every 2 weeks in addition to treatment as usual. No oral antipsychotics were permitted after the first 3 weeks of the open-label phase. Patients meeting criteria for stable remission throughout the last 4 weeks of the stabilization phase were then eligible to enter the double-blind maintenance phase for up to 52 weeks. The primary outcome measure was the time to relapse, as verified by an independent monitoring board. The majority of enrolled participants were male (69%), of Indian ethnicity (82%), and were diagnosed with the bipolar I subtype (90%).[27]

Another unpublished, double-blind, placebo-controlled, relapse-prevention trial was also conducted with LAR in bipolar I disorder, this time lasting for up to 24 months.[28] After receiving oral risperidone for 3 weeks, patients were enrolled into a 26-week stabilization phase during which open-label LAR was administered. Dosing was flexible and ranged from 12.5-50 mg of LAR every 2 weeks. Patients maintaining a treatment response during the last 8 weeks of open-label stabilization subsequently entered the double-blind treatment phase and were randomized to their current dose of LAR or i.m. placebo.[28] The efficacy and safety data from both of these pivotal trials have not yet been published. However, based on the results of these two studies, in May 2009 the US FDA approved LAR as both a monotherapy and adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder.

DISCUSSION

Treatment Adherence

Nearly a third of bipolar patients may miss 30% or more of their prescribed medication each month.[29] Additionally, partially adherent

or nonadherent individuals encompass at least half, if not more, of all patients with bipolar disorder.[11] Given that depot antipsychotic formulations maintain more stable plasma drug concentrations and reduce the risk of inadvertent excess dosing when compared with oral formulations, they may comprise viable treatment alternatives for patients at greater risk of noncompliance, such as younger patients and those with comorbid substance-abuse disorders.[11] These populations should be avidly recruited into future clinical trials given that LAR has not been studied in adolescents with bipolar disorder or in those actively abusing or dependent on alcohol or illicit substances. Furthermore, implementation of strategies capable of improving adherence presage clinical outcomes, as medication nonadherence remains a modifiable barrier in the management of bipolar disorder. Improved adherence has implications for symptomatic, functional, humanistic (eg, quality of life), as well as service utilization outcomes.[30]

Notwithstanding the compliance enhancement implications of LAR, patients are still required to adhere to biweekly administration of this formulation. Although satisfaction with LAR was significantly improved compared with prior treatment in patients with schizophrenia,[31] a 3-year observational study found that 84% of patients discontinued LAR within 3 years.[32] In this mixed sample of 211 patients with schizophrenia, bipolar disorder, and other psychiatric diagnoses, patient choice and ineffectiveness accounted for more than 70% of discontinuations.

Relapse Prevention with Atypical Antipsychotics

During the past decade, there has been substantial progress in developing pharmacological treatments for acute bipolar mania. However, there are relatively fewer studies that have sufficiently evaluated pharmacological (and psychosocial) treatments during the maintenance phase. In 2007, the Canadian Network for Mood and Anxiety Treatments (CANMAT) synthesized available evidence by establishing guidelines for the long-term management of bipolar disorder.[8] The CANMAT guidelines recommended the use of lithium, lamotrigine, olanzapine, and divalproex as first-line options. These recommendations cohered with the Texas Implementation of Medication Algorithms (TIMA) published in 2005, except that TIMA guidelines relegated olanzapine to a second-line choice due to safety concerns with its long-term use.[33] As illustrated by a 47-week maintenance study comparing olanzapine with valproate, olanzapine demonstrated superiority in preventing new symptoms of mania, but contributed to greater increases in body weight and total cholesterol, effectively narrowing the risk:benefit ratio.[9]

Since the publication of these treatment guidelines, other maintenance trials have been completed that demonstrate the efficacy of both quetiapine and LAR in preventing relapse into a new mood episode. The efficacy of quetiapine at relapse prevention is supported both as monotherapy[34] and adjunctive therapy in combination with lithium or valproate.[35,36] Published results are available from two multicenter, adjunctive maintenance trials that evaluated quetiapine in combination with lithium or valproate during a 12-36 week stabilization phase, followed by a randomized, double-blind, placebo-controlled phase lasting up to 2 years.[35,36] Pooled study results showed an approximately 70% lower risk in the time to recurrence of a mood event over placebo when quetiapine was combined with lithium or valproate.[37] The 2009 iteration of the CANMAT bipolar guidelines now recommend

LAR, quetiapine, and ziprasidone as maintenance treatments.[38]

Apart from olanzapine, quetiapine, and LAR, the dopamine partial agonist, aripiprazole, remains the only other atypical antipsychotic to demonstrate efficacy over the maintenance phase. Aripiprazole significantly delayed the time to relapse into a new mood episode in patients with bipolar I disorder over both 26 and 100 weeks of treatment.[10,39] The favorable metabolic profile of aripiprazole may also offer a safety advantage over other compounds in this class, as the rate of metabolic syndrome did not increase over 26 weeks of treatment.[40] Complete data on all five parameters of metabolic syndrome have not been reported for LAR.

The Role of Combination Therapy

Even in the context of receiving evidence-based treatment, patients with rapid-cycling bipolar disorder (four or more mood episodes over the last 12 months) are more likely to experience mood recurrences and are less likely to achieve stabilization.[41] Residual mood symptoms also serve as powerful predictors of recurrence, particularly for episodes toward the depressive pole.[42] In such patients with rapid-cycling or residual mood symptoms, monotherapy is largely ineffective and often requires combination treatment as the standard of care.[43] Indeed, extant research has shown rates of response to be 20% higher when atypical antipsychotics are used in combination with lithium or valproate than when used alone.[44] Combining an atypical antipsychotic with a conventional mood stabilizer has now been shown to be an effective strategy for relapse prevention with olanzapine, quetiapine, and LAR. However, only LAR has been specifically studied in frequently relapsing (ie, rapid-cycling) bipolar disorder.

Limitations

The large-scale trials involving LAR as discussed in this report have been presented at national meetings, but they have not yet undergone peer review.[27,28] More importantly, no inferences can be made as to the acute antimanic or antidepressant properties of LAR, given the inadequate sample sizes of available studies. Although oral risperidone rapidly controls the symptoms of mania, it has not been shown to have antidepressant effects in treatment-resistant bipolar depression,[45] suggesting that LAR may likewise lack acute antidepressant efficacy. Furthermore, LAR was not associated with a decrease in the rate of hospitalizations due to depressive episodes in one observational study,[25] and it is unknown whether a significant improvement in depressive symptoms occurred among patients enrolled in the longer-term trials of LAR designed for regulatory approval.[27,28] There is currently no evidence to suggest that LAR demonstrates an advantage over other atypical antipsychotics, as head-to-head comparisons have not yet been conducted. LAR has been shown to be effective at a dose of 25 mg every 2 weeks in bipolar disorder, but there is obscurity as to the clinical utility of the 25 mg dose in certain populations.[32,46,47] Consequently, it may be premature to speculate on the optimal dosing of LAR in heterogeneous clinical trial populations with bipolar disorder. Additional limitations of extant studies include the small numbers of participants enrolled with bipolar II disorder and the sizable proportion of patients of Indian ethnicity. These design variables have the potential to produce unique effect sizes and reduce generalizability.[48]

Despite the beneficial effect on psychiatric symptoms, the longer-term metabolic and safety risks still await examination. The metabolic safety of atypical antipsychotics may

be particularly pertinent to younger patients, where treatment with oral risperidone and olanzapine were recently shown not to demonstrate superior efficacy over molindone for early-onset schizophrenia and schizoaffective disorder.[49] The safety findings related to weight gain and metabolic problems raise important public health concerns for long-term risks of diabetes and cardiovascular disease in a population already at increased risk for premature mortality due to general medical conditions. The risk for adverse effects that do not typically manifest until after years of sustained use, such as tardive dyskinesia, is also indeterminate.

Presently, risperidone is the only atypical antipsychotic currently available as a long-acting, injectable preparation. Studies of paliperidone extended-release (ER), the major active metabolite of risperidone, are currently underway to evaluate its ability to prevent recurrences of mood symptoms in patients with an acute manic or mixed episode who initially responded to paliperidone ER.[50] Another long-acting atypical antipsychotic, the pamoate formulation of olanzapine, has been delayed from release due to safety concerns related to postinjection delirium sedation, requiring patients to be observed for 3 hours after injection.[51]

CONCLUSION

Given recent FDA approval for the maintenance phase of bipolar I disorder, LAR is now the first long-acting, atypical antipsychotic therapy available for the treatment of both schizophrenia[52] and bipolar disorder. Results from several open-label and double-blind trials in patients with bipolar disorder have found LAR to be well tolerated, but to produce elevated rates of EPS and varied metabolic disturbances. Once the safety outcomes have been released from the 12- and 24-month relapse prevention trials of LAR, careful scrutiny will be required of its effects on body weight, glucose regulation, and prolactin concentrations. At present, LAR appears to be a viable alternative for patients who are noncompliant with oral atypical antipsychotic therapy, and it represents an additional psychopharmacologic option in the maintenance treatment of bipolar disorder, for which more safe and efficacious treatments are urgently needed.

ACKNOWLEDGMENTS

Dr. Kemp has acted as a consultant to Bristol-Myers Squibb, has received research grants from NARSAD, and has served on a speaker's bureau for Pfizer. This work was supported in part by NIH grant 1KL2RR024990 and by the International Society for Bipolar Disorders Research Fellowship Award to Dr. Kemp. Dr. Canan has no relevant disclosures to report. Dr. Goldstein has received grants from the American Foundation for Suicide Prevention and NARSAD. Dr. McIntyre has received grants from Eli Lilly, NARSAD, and the Stanley Medical Research Institute; has served on the advisory boards for AstraZeneca, Bristol-Myers Squibb, France Foundation, GlaxoSmithKline, Janssen-Ortho, Solvay/Wyeth, Eli Lilly, Organon, Lundbeck, Biovail, Pfizer, and Shire; served on the speaker's bureau for Janssen-Ortho, Astra-Zeneca, Eli Lilly, Lundbeck, and Biovail; and has participated in CME activities with AstraZeneca, Bristol-Myers Squibb, France Foundation, I3CME, Solvay/Wyeth, and Physicians' Postgraduate Press.

REFERENCES

1. Goodwin FK, Jamison KR. Manic-Depressive Illness. 2nd edition. New York, NY: Oxford University Press; 2007.

2. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990 to 2003. N Engl J Med. 2005;352:2515-2523.

3. Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. Bull World Health Organ. 1994;72:495-509.

4. Simon GE, Bauer MS, Ludman EJ, Operskalski BH, Unutzer J. Mood symptoms, functional impairment, and disability in people with bipolar disorder: specific effects of mania and depression. J Clin Psychiatry. 2007;68:1237-1245.

5. Osby U, Brandt L, Correla N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry. 2001;58:844-850.

6. Miller BJ, Paschall CB 3rd, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. Psychiatr Serv. 2006;57:1482-1487.

7. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34-38 years. J Affect Disord. 2002;68:167-181.

8. Yatham LN, Kennedy SH, O'Donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007. Bipolar Disord. 2006;6:721-739.

9. Tohen M, Ketter TA, Zarate CA, et al. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry. 2003;160:1263-1271.

10. Keck PE, Jr., Calabrese JR, McQuade RD, 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;67:626-637.

11. Sajatovic M, Valenstein M, Blow FC, Ganoczy D, Ignacio RV. Treatment adherence with antipsychotic medications in bipolar disorder. Bipolar Disord. 2006;8:232-231.

12. Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry. 2002;47:27-38.

13. Eerdekens M, Van Hove I, Remmerie B, Mannaert E. Pharmacokinetics and tolerability of long-acting risperidone in schizophrenia. Schizophr Res. 2004;70:91-100.

14. Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry. 2003;160:1125-1132.

15. Risperdal Consta (risperidone) long-acting injection. Prescribing information. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2008.

16. Hirschfeld RM, Keck PE Jr, Kramer M, et al. Rapid antimanic effect of risperidone monotherapy: a 3-week multicenter, double-blind, placebo-controlled trial. Am J Psychiatry. 2004;161:1057-1065.

17. Smulevich AB, Khanna S, Eerdekens M, Karcher K, Kramer M, Grossman F. Acute and continuation risperidone monotherapy in bipolar mania: a 3-week placebo-controlled trial followed by a 9-week double-blind trial of risperidone and haloperidol. Eur Neuropsychopharmacol. 2005;15:75-84.

18. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. Bipolar Disord. 2007;6:551-560.

19. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry. 2002;159:1146-1154.

20. Yatham LN, Grossman F, Augustyns I, Vieta E, Ravindran. Mood stabilizers plus risperidone or placebo in the treatment of acute mania. Br J Psychiatry. 2003;182:141-147.

21. Khanna S, Vieta E, Lyons B, Grossman F, Eerdekens M, Kramer M. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. Br J Psychiatry. 2005;187:229-234.

22. Savas HA, Mehmet Y, Murat EO. Use of long-acting risperidone in the treatment of bipolar patients. J Clin Psychopharmacol. 2006;26:530-531.

23. Han C, Lee M, Pae C, Ko Y, Patkar AA, Jung I. Usefulness of long-acting injectable risperidone during 12-month maintenance therapy of bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:1219-1223.

24. Malempati RN, Bond DJ, Yatham LN. Depot risperidone in the outpatient management of bipolar disorder: a 2-year study of 10 patients. Int Clin Psychopharmacol. 2008;23:88-94.

25. Vieta E, Nieto E, Autet A, et al. A long-term prospective study on the outcome of bipolar patients treated with long-acting injectable risperidone. World J Biol Psychiatry. 2008;23:1-6.

26. Yatham LN, Fallu A, Binder CE. A 6-month randomized open-label comparison of continuation

of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. Acta Psychiatr Scand Suppl. 2007;116:50-56.

27. Kujawa M, Turner N, Turkoz I, et al. Frequently relapsing bipolar disorder: evidence for an effective treatment. Presented at: 14th Biennial Winter Workshop on Schizophrenia and Bipolar Disorders; Montreux, Switzerland; February 3-7, 2008.

28. Johnson & Johnson Pharmaceutical Research & Development, LLC. 2008. Clinical Trials website. A study of the safety and efficacy of injectable risperidone in the prevention of bipolar mood episodes (NCT00132678). Available at: http://clinicaltrials.gov/ct2/show/NCT00132678. Accessed October 15, 2008.

29. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry. 2002;635:384-390.

30. Gianfrancesco FD, Sajatovic M, Rajagopalan K, Wang RH. Antipsychotic treatment adherence and associated mental health care use among individuals with bipolar disorder. Clin Ther. 2008;30:1358-1374.

31. Freyberger HJ, Eerdekens M, Duchesne I, et al. Patient satisfaction with their medication during long-acting risperidone injection. Int J Neuropsychopharmacol. 2002;5(suppl. 1):189. Abstract.

32. Taylor DM, Fischetti C, Sparshatt A, Thomas A, Bishara D, Cornelius V. Risperidone long-acting injection: a prospective 3-year analysis of its use in clinical practice. J Clin Psychiatry. 2009;70:196-200.

33. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry. 2005;667:870-886.

34. Young A, McElroy S, Olausson B, et al. Quetiapine monotherapy up to 52 weeks in patients with bipolar depression: continuation phase data from EMBOLDEN I & II. Presented at: 21st ENCP Conference; Barcelona, Spain; August 30-September 3, 2008.

35. Vieta E, Suppes T, Eggans I, et al. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126). J Affect Disord. 2008;109:251-263.

36. Suppes T, Vieta E, Liu S, et al. Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex (trial 127). Am J Psychiatry. 2009;166:476-488.

37. Brecher M, Anderssen H, Paulsson P. Quetiapine in the maintenance treatment of bipolar I disorder: combined data from two long-term, phase III studies (NR 3-007). New Research Abstracts. Presented at: Annual Meeting of the American Psychiatric Association 2008; Washington, DC, USA; May 3, 2008.

38. Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11:225-255.

39. Keck PE Jr., Calabrese JR, McIntyre RS, et al. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry. 2007;68:1480-1491.

40. Kemp DE, Calabrese JR, Van-Tran Q, et al. Components of metabolic syndrome in patients enrolled in a clinical trial of aripiprazole for the maintenance treatment of bipolar disorder. Presented at: American College of Neuropsychopharmacology Annual Meeting; Boca Raton, FL; Dec. 9-13, 2007.

41. Schneck CD, Miklowitz DJ, Miyahara S, et al. The prospective course of rapid-cycling bipolar disorder: findings from the STEP-BD. Am J Psychiatry. 2008;1653:370-377.

42. Perlis RH, Ostacher MJ, Patel, JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2006;1632:217-224.

43. Tondo L, Hennen J, Baldessarini RJ. Rapid-cycling bipolar disorder: effects of long-term treatments. Acta Psychiatr Scand. 2003;108:4-14.

44. Yatham LN. Atypical antipsychotics for bipolar disorder. Psychiatr Clin North Am. 2005;28:325-347.

45. Nierenberg AA, Ostacher MJ, Calabrese JR. 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.

46. Taylor D. Risperidone long-acting injection practice: more questions than answers? Acta Psychiatr Scand. 2006;114:1-2.

47. Bai YM, Ting Chen T, Chen JY, et al. Equivalent switching dose from oral risperidone to risperidone long-acting injection: a 48-week randomized, prospective single-blind pharmacokinetic study. J Clin Psychiatry. 2007;68:1218-1225.

48. Calabrese JR, Kemp DE. Bipolar drug development: are we getting closer to the real world? Am J Psychiatry. 2008;165:1234-1236.

49. Sikich L, Frazier JA, McClellan J, et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizoaffective disorder: findings from the Treatment of Early-Onset Schizophrenia Spectrum Disorders (TEOSS) Study. Am J Psychiatry. 2008;165:1420-1431.

50. Clinical Trials website. A study to evaluate the effectiveness and safety of extended-release (ER) paliperidone compared with placebo in delaying the recurrence of symptoms in bipolar I disorder. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00490971?term=paliperidone+ER+bipolar&rank=3. Accessed December 21, 2008.

51. Citrome L. Olanzapine pamoate: a stick in time? A review of the efficacy and safety profile of a new depot formulation of a second-generation antipsychotic. Int J Clin Pract. 2009;63:140-150.

52. Harrison TS, Goa KL. Long-acting risperidone: a review of its use in schizophrenia. CNS Drugs. 2004;18:113-132.