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Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: A CANMAT randomized double-blind trial

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ORIGINAL ARTICLE

Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: A CANMAT randomized double-blind trial

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Atypical antipsychotic adjunctive therapy to lithium or valproate is effective in treating acute mania. Although continuation of atypical antipsychotic adjunctive therapy after mania remission reduces relapse of mood episodes, the optimal duration is unknown. As many atypical antipsychotics cause weight gain and metabolic syndrome, they should not be continued unless the benefits outweigh the risks. This 52-week double-blind placebo-controlled trial recruited patients with bipolar I disorder ($n = 159$) who recently remitted from a manic episode during treatment with risperidone or olanzapine adjunctive therapy to lithium or valproate. Patients were randomized to one of three conditions: discontinuation of risperidone or olanzapine and substitution with placebo at (i) entry ('0-weeks' group) or (ii) at 24 weeks after entry ('24-weeks' group) or (iii) continuation of risperidone or olanzapine for the full duration of the study ('52-weeks' group). The primary outcome measure was time to relapse of any mood episode. Compared with the 0-weeks group, the time to any mood episode was significantly longer in the 24-weeks group (hazard ratio (HR) 0.53; 95% confidence interval (CI): 0.33, 0.86) and nearly so in the 52-weeks group (HR: 0.63; 95% CI: 0.39, 1.02). The relapse rate was similar in the 52-weeks group compared with the 24-weeks group (HR: 1.18; 95% CI: 0.71, 1.99); however, sub-group analysis showed discordant results between the two antipsychotics (HR: 0.48, 95% CI: 0.17; 1.32 olanzapine patients; HR: 1.85, 95% CI: 1.00, 3.41 risperidone patients). Average weight gain was 3.2 kg in the 52-weeks group compared with a weight loss of 0.2 kg in the 0-weeks and 0.1 kg in the 24-weeks groups. These findings suggest that risperidone or olanzapine adjunctive therapy for 24 weeks is beneficial but continuation of risperidone beyond this period does not reduce the risk of relapse. Whether continuation of olanzapine beyond this period reduces relapse risk remains unclear but the potential benefit needs to be weighed against an increased risk of weight gain.

INTRODUCTION

Bipolar I disorder is a lifelong condition characterized by manic and depressive episodes. A significant proportion of patients experiencing an acute manic episode are treated with a combination of a mood stabilizer (that is, lithium or valproate) and an atypical antipsychotic.[1,2] There is general consensus as indicated by recommendations from various guidelines about continuing a mood stabilizer to reduce the risk of relapse or recurrence of a mood episode.[3–5] In addition, there is also evidence from some[6–9] but not all[10] studies that continuation of an atypical antipsychotic as an adjunct to a mood stabilizer provides additional benefit in reducing the risk of relapse but the

optimal duration of such strategy remains unknown. For instance, different industry-funded registration trials have reported continuation of an atypical antipsychotic as being beneficial, compared with placebo, when given as adjunct for 6 months,[9] 12 months[8] or 24 months.[6,7] However, none of these studies examined different durations for the atypical antipsychotic therapy within the same trial. An examination of survival curves from these trials suggests that most relapses in the placebo adjunctive therapy group occurred within the first 6 months of randomization. Does this mean that the atypical antipsychotic adjunctive therapy is beneficial mainly within the first 6 months of remission of an acute mood episode and not beyond? This is a critical question because atypical antipsychotics are associated

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with significant side effects such as weight gain, metabolic syndrome and extrapyramidal side effects and hence should not be continued unless their benefits beyond 6 months can be clearly demonstrated.

Therefore, the primary objective of this randomized double-blind placebo-controlled trial was to determine the efficacy of different durations (24 or 52 weeks) of atypical antipsychotic adjunctive therapy (that is, risperidone or olanzapine) to mood stabilizer vs discontinuing the atypical antipsychotic at study entry in preventing relapse of any mood episode in bipolar I disorder patients who recently remitted (within 6 weeks of remission) from an acute manic episode. An important additional objective was to investigate whether 52 weeks of treatment offered any additional benefit compared with discontinuing the atypical antipsychotic after 24 weeks.

MATERIALS AND METHODS

Subjects

Patients for the study were recruited from 17 Canadian Network for Mood and Anxiety Treatments (CANMAT)-affiliated academic centers in Canada and collaborating sites in Brazil. Study procedures were approved by the Research Ethics Boards of each site. A written informed consent was obtained from all patients after providing a complete description of the study. Patients aged ⩾ 17 years were eligible for the study if they were: (1) diagnosed with Bipolar I disorder; (2) treated within the previous 12 weeks, for a DSM-IV[11] acute manic or mixed episode with a combination of mood stabilizer (lithium or valproate) and atypical antipsychotic (risperidone or olanzapine); (3) in remission from the manic or mixed episode for at least 2 weeks and no more than 6 weeks based on (i) a Clinical Global Impression Severity (CGI-S)[12] score of 2 or less for 2 consecutive weeks or (ii) a Young Mania Rating Scale (YMRS)[13] score of 8 or less and a Hamilton Rating Scale for Depression (HAM-D)[14] 21- item score of 8 or less for two consecutive weeks.

Patients with a history of comorbid substance abuse or other axis I disorders were allowed but those taking other psychotropic medication with the exception of benzodiazepines were excluded.

Trial design and interventions

This study was a multi-center three-parallel-group randomized double-blind placebo-controlled trial with up to 52 weeks of follow-up. After obtaining informed consent, patients were randomized to one of the three groups. Randomizations were stratified by drug combination and by center. The treating clinicians and all research personnel except the trial statistician and the pharmacist were blinded to treatment arm allocations. Patients randomized to the '0-weeks' group tapered and discontinued risperidone or olanzapine over 2 weeks beginning on the day of randomization and received placebo substitution for the remaining 50 weeks. Patients randomized to the '24-weeks' group received risperidone or olanzapine for 24 weeks. The antipsychotic was tapered and discontinued over the next 2 weeks with the placebo substitution for the remaining 26 weeks. Patients randomized to the '52-weeks' group continued risperidone or olanzapine for 52 weeks. All patients continued the same mood stabilizer (lithium or valproate) they had been taking at study entry and serum levels were maintained within the therapeutic ranges (0.6–1.2 mmol/L for lithium and 350–830 μmol/L for valproate) throughout the 52 weeks. The dose and type of atypical antipsychotic were the same as the patient had been on at entry into the study. Allowed dosages for risperidone were 1–6 mg per day and olanzapine 5–25 mg per day. Patients were not allowed to receive any other psychotropic medication except benzodiazepines for sedation and anti-parkinsonian medication for extrapyramidal side effects. Patients were allowed to receive psychoeducation and counseling regarding sleep hygiene, healthy daily routines and rhythms, alcohol and substance abuse, anxiety management, conflict resolution and problem solving, as clinically indicated as part of their ongoing clinical care.

Study outcomes

Patients were assessed biweekly until week 8 and every 4 weeks thereafter up to week 52 by trained raters blind to treatment allocation using the following instruments: YMRS, HAMD-21, Montgomery-Asberg Depression Rating Scale (MADRS),[15] CGI-S and Clinical Global Impression-Bipolar Severity (CGI-BP). Clinical Global Impression-Improvement (CGI-I) and CGI-BP change were assessed from week 2 onwards. Safety and tolerability were evaluated through clinical observation as well as using the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU)[16] as well as the Extrapyramidal Symptoms Rating Scale (ESRS)[17] at baseline and at monthly visits. Laboratory measurements on blood sera were obtained at the screening visit and at weeks 12, 24, 36 and 52.

The primary outcome measure was the time to any mood episode, defined as any of the following events: (i) YMRS score of 15 or greater, (ii) HAM-D 21-item score of 15 or greater or HAM-D suicide item score of 3 or greater, (iii) CGI-S score of 3 or greater, (iv) hospitalization for treatment of mood symptoms or (v) suicide or suicide attempt. Patients experiencing a primary event were removed from further study follow-up.

Secondary outcome measures were time to a manic episode, time to a depressive episode and time to premature discontinuation from the study for any clinical reason (primary endpoint met, dose change in risperidone or olanzapine study medication, new intervention, adverse event). Primary outcome events were classified as manic or depressive based on the CGI-BP, YMRS and HAM-D scores.

Sample size

The planned sample size for the trial was 540 patients (180 per group). This sample size was based on two primary comparisons of the event proportions (24-weeks vs 0-weeks groups and 52-weeks vs 0-week groups) by 52 weeks, each at a two-sided significance level of 0.025 (to ensure an overall type I error rate less than 5%) with 80% power and allowing for a 25% drop-out rate. The assumed event proportions were 55% in the 0-week group and 38% (that is, absolute reduction of 17%) in each of the other two groups.

Statistical analysis

All analyses were conducted on an intent-to-treat basis and included all randomized patients. Kaplan–Meier cumulative incidence plots were used to summarize the time to any mood episode by treatment group. For the primary analysis, a Cox proportional hazards model with adjustment for the antipsychotic drug and for the mood stabilizer drug was used to compare the time to any mood episode across treatment groups. As a sensitivity analysis, a mixed effects (frailty) Cox model with site entered as a clustering variable was fit to account for potential site effects. Patients who did not experience the primary outcome were censored as of the time of last follow-up visit.

Similar analyses were used to evaluate the time to a manic episode, and the time to a depressive episode. When analyzing the time to a manic (depressive) event, patients experiencing a depressive event (manic event) were censored at the time of this event.

Changes in weight and laboratory parameters were calculated as the difference between the measurements at baseline and at last follow-up; if the measurement at last follow-up was missing, the most recently observed value was used.

RESULTS

Patients and disposition

A total of 159 patients were randomized (52 to the 0-weeks group, 54 to the 24-weeks group and 53 to the 52-weeks group) into the trial across 17 sites. The recruitment for the study was much slower than anticipated and ultimately was stopped because of expiration of funding.

Patient characteristics were well-balanced across the groups except that the patients in the 0-weeks group had a higher percentage of women, lower mean weight and lower percentage with a history of or currently active psychiatric comorbidity compared with the patients in the other two groups, while the patients in the 24-weeks group had a lower percentage with alcohol/substance abuse (Table 1). The disposition of patients is summarized in Figure 1. A total of 34 (21%) patients discontinued the study (8, 14 and 12 patients in the 0-weeks, 24-weeks and 52-weeks groups, respectively) for reasons other than meeting the primary endpoint. The mean follow-up times were 18, 25 and

Table 1. Baseline patient characteristics

	0 weeks (N = 52[a])	24 weeks (N = 54[b])	52 weeks (N = 53[c])	All (N = 159)
	N (%)	N (%)	N (%)	N (%)
Male	20 (38%)	28 (53%)	31 (58%)	79 (50%)
Race				
Caucasian	45 (86%)	40 (74%)	40 (75%)	125 (79%)
Asian	3 (6%)	4 (8%)	3 (6%)	10 (6%)
Black	2 (4%)	4 (8%)	6 (11%)	12 (8%)
Hispanic	0 (0%)	4 (8%)	1 (2%)	5 (3%)
Other	2 (4%)	1 (2%)	3 (6%)	6 (4%)
Alcohol/substance abuse comorbidity	23 (44%)	17 (31%)	22 (42%)	62 (39%)
Other psychiatric comorbidity	9 (17%)	15 (28%)	17 (32%)	41 (26%)
Episode type				
Manic	43 (83%)	45 (83%)	43 (81%)	131 (82%)
Mixed	9 (17%)	9 (17%)	10 (19%)	28 (18%)
Drug combination, n (%)				
Lithium+Olanzapine	10 (19%)	10 (19%)	11 (20%)	31 (19%)
Lithium+Risperidone	17 (33%)	19 (35%)	18 (34%)	54 (34%)
Epival+Olanzapine	12 (23%)	11 (20%)	12 (23%)	35 (22%)
Epival+Risperidone	13 (25%)	14 (26%)	12 (23%)	39 (25%)
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)
Age (year)	38.96 (15.43)	38.13 (13.59)	36.66 (11.32)	37.91 (13.49)
Weight (kg)	71.58 (11.48)	84.56 (23.74)	84.42 (19.60)	80.33 (19.90)
Duration of bipolar disorder (year)	10.56 (11.70)	10.98 (11.27)	11.71 (10.27)	11.08 (11.04)
Lithium levels (mmol/L)	0.79 (0.19)	0.81 (0.16)	0.79 (0.24)	0.80 (0.20)
Valproate levels (μmol/L)	469.19 (139.68)	484.47 (111.08)	504.25 (113.68)	485.47 (121.53)
Olanazpine dose (mg)	10.11 (4.53)	10.60 (5.64)	9.57 (4.44)	10.08 (4.82)
Risperidone dose (mg)	2.08 (1.10)	2.38 (1.41)	2.45 (1.46)	2.31 (1.33)

Abbreviation: s.d., standard deviation. [a]One patient missing weight; two patients missing lithium level. [b]One patient missing age, gender, race; two patients missing lithium level. [c]One patient missing valproate level and duration of bipolar disorder.
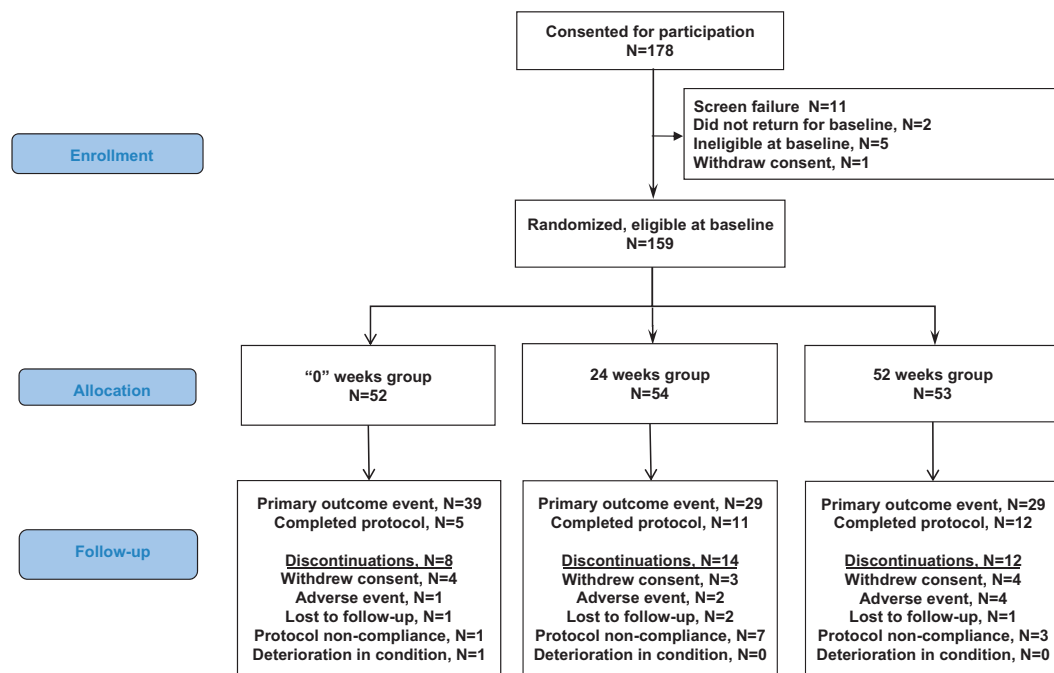

Figure 1. Subject enrollment and disposition.

	Treatment group		
Table 2. Primary events by criterion and in antipsychotic sub-groups	0 weeks N = 52	24 weeks N = 54	52 weeks N = 53
Total:	39	29	29
By study criterion[a]:			
YMRS score of 15 or greater	10	5	7
HAM-D 21-item score of 15 or greater	16	13	14
HAM-D suicide item score of 3 or greater	4	5	2
CGI-S score of 3 or greater	38	27	29
Patient required hospitalization	8	1	3
Patient who made a suicide attempt or committed suicide	0	0	0
Antipsychotic sub-groups			
Olanzapine	N = 22	N = 21	N = 23
Mania	3	4	3
Depression	12	6	3
Risperidone	N = 30	N = 33	N = 30
Mania	11	2	4
Depression	13	17	19

Abbreviations: CGI-S, Clinical Global Impression Severity; HAM-D, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale. [a]Patients may have met more than one criterion for a primary event.

24 weeks for the 0-weeks, 24-weeks and 52-weeks groups, respectively.

Primary outcomes

There were 39 primary events (depression = 25, mania = 14) among 52 patients in the 0-weeks group, 29 events (depression = 23, mania = 6) among 54 patients in the 24-weeks group and 29 (depression = 22, mania = 7) events among 53 patients in the 52-weeks group (Table 2). Kaplan–Meier cumulative incidence curves (Figure 2a) suggested that the time to any mood episode was longer in both 52-weeks and 24-weeks groups compared with the 0-weeks group. However, the time to any mood episode was similar between the 52-weeks and 24-weeks groups. In the adjusted Cox analysis, the hazard ratio (HR) for time to any mood episode was 0.53 for the 24-weeks group relative to the 0-weeks group (95% confidence interval (CI): 0.33, 0.86; $P = 0.01$) and 0.63 for the 52-weeks group relative to the 0-weeks group (95% CI: 0.39, 1.02; $P = 0.06$). The HR for the 52-weeks group relative to the 24-weeks group was 1.18 (95% CI: 0.71, 1.99; $P = 0.52$). On the basis of the Kaplan–Meier curves, the estimated 52-week event rates were 65%, 65% and 87% in the 52-weeks, 24-weeks and 0-weeks groups, respectively. The results were negligibly different in the mixed effects Cox model accounting for clustering by site.

Secondary outcomes

Across groups, a total of 27 patients met criteria for a manic event and 70 for a depressive event. The time to a manic episode was longer in patients randomized to the 24-weeks and the 52-weeks groups compared with patients randomized to the 0-weeks group (Figure 2b) and statistically significant for the 24-weeks group (HR: 0.30, 95% CI: 0.12, 0.80; $P = 0.02$) but not for the 52-weeks group (HR: 0.43, 95% CI: 0.17, 1.09; $P = 0.08$). The time to a manic episode was shorter in the 52-weeks group compared with the 24-weeks groups but the difference was not statistically significant (HR: 1.41, 95% CI: 0.47, 4.25, $P = 0.54$).

Although the time to a depressive episode was also longer in the 24-weeks and 52-weeks groups compared with the 0-weeks group (Figure 2c), this difference was not statistically significant

for either group (HR for 24-weeks vs 0-weeks groups: 0.65; 95% CI: 0.37, 1.15, $P = 0.14$: HR for 52-weeks vs 0-weeks groups: 0.73; 95% CI: 0.41, 1.29, $P = 0.28$). In addition, the time to a depressive episode was similar in the 52-weeks group compared with the 24-weeks group (HR: 1.11; 95% CI: 0.62, 2.01, $P = 0.72$).

The time to discontinuation for any clinical reason was longer in the 24-weeks and the 52-weeks groups compared with the 0-weeks group, but the effect was statistically significant only for the 24-weeks group (HR: 0.54, 95% CI: 0.34, 0.86, $P = 0.01$) but not for the 52-weeks group (HR: 0.65, 95% CI: 0.41, 1.04, $P = 0.07$). The time to discontinuation for any clinical reason was similar in the 52-weeks group compared with the 24-weeks group (HR: 1.22, 95% CI: 0.74, 1.99, $P = 0.44$).

Subgroup analysis. In the olanzapine subgroup, the time to any mood episode was longer in both the 24-weeks and the 52-weeks groups compared with the 0-weeks group, with the difference reaching statistical significance for the 52-week group (HR: 0.23, 95% CI: 0.09, 0.59, $P = 0.003$) but not for the 24-weeks group (HR: 0.47, 95% CI: 0.21, 1.07, $P = 0.07$). The time to any mood episode was longer but not statistically significant in the 52-weeks group compared with the 24-weeks group (HR: 0.48, 95% CI: 0.17; 1.32, $P = 0.16$).

In the risperidone subgroup, the time to any mood episode was longer in the 24-weeks group relative to 0-weeks group but was not statistically significant (HR: 0.57, 95% CI: 0.31, 1.05, $P = 0.07$). Surprisingly, the time to any mood episode in the 52-week group was similar to that in the 0-weeks group (HR: 1.05, 95% CI: 0.59, 1.88, $P = 0.86$) and shorter than in the 24-weeks group (HR: 1.85, 95% CI: 1.00, 3.41; $P = 0.05$).

Adverse events

The only serious adverse event recorded was the single death from pneumonia, which occurred in the 52-weeks group, and was determined by the site investigator as being unrelated to the study medication. Rates of other adverse events were similar across the three groups (Table 3). The mean changes in the ESRS total score, Parkinsonism+Dystonia subscale and Dyskinesia subscale were similar across all three groups.

In terms of weight change, patients in the 52-weeks group gained significantly more weight (3.2 kg, $P = 0.01$) compared with those in the 0-weeks group (lost 0.2 kg) and 24-weeks group (lost 0.1 kg). Within the olanzapine subgroup, the weight changes were a loss of 0.7 kg, a loss of 0.2 kg and a gain of 5.6 kg in the 0-week, 24-week and 52-week groups, respectively. The corresponding weight changes in the risperidone subgroup were a gain of 0.3 kg, no change and a gain of 1.3 kg. Clinically significant weight gain (⩾7% or more of baseline weight) was more common among patients in the 52-weeks group (25%) than in the 0-weeks (12%) and 24-weeks (15%) groups. In the olanzapine subgroup, more patients gained ⩾7% weight in the 52-weeks group (35%) compared with the 0-weeks group (5%) or the 24-weeks group (14%), while in the risperidone subgroup, these proportions were more similar across the groups (17%, 15% and 17% in the 0-weeks, 24-weeks and 52-weeks groups, respectively). Average change in glucose, cholesterol or triglycerides levels from baseline to last follow-up were similar in all three groups whether including all patients or in either antipsychotic subgroup.

DISCUSSION

This is the first study to compare different durations of atypical antipsychotic adjunctive therapy in the maintenance treatment of bipolar I disorder after remission from an acute manic or mixed episode. The most important findings of the study are: (i) The time to relapse of any mood episode was significantly longer in the group that continued atypical antipsychotic adjunctive
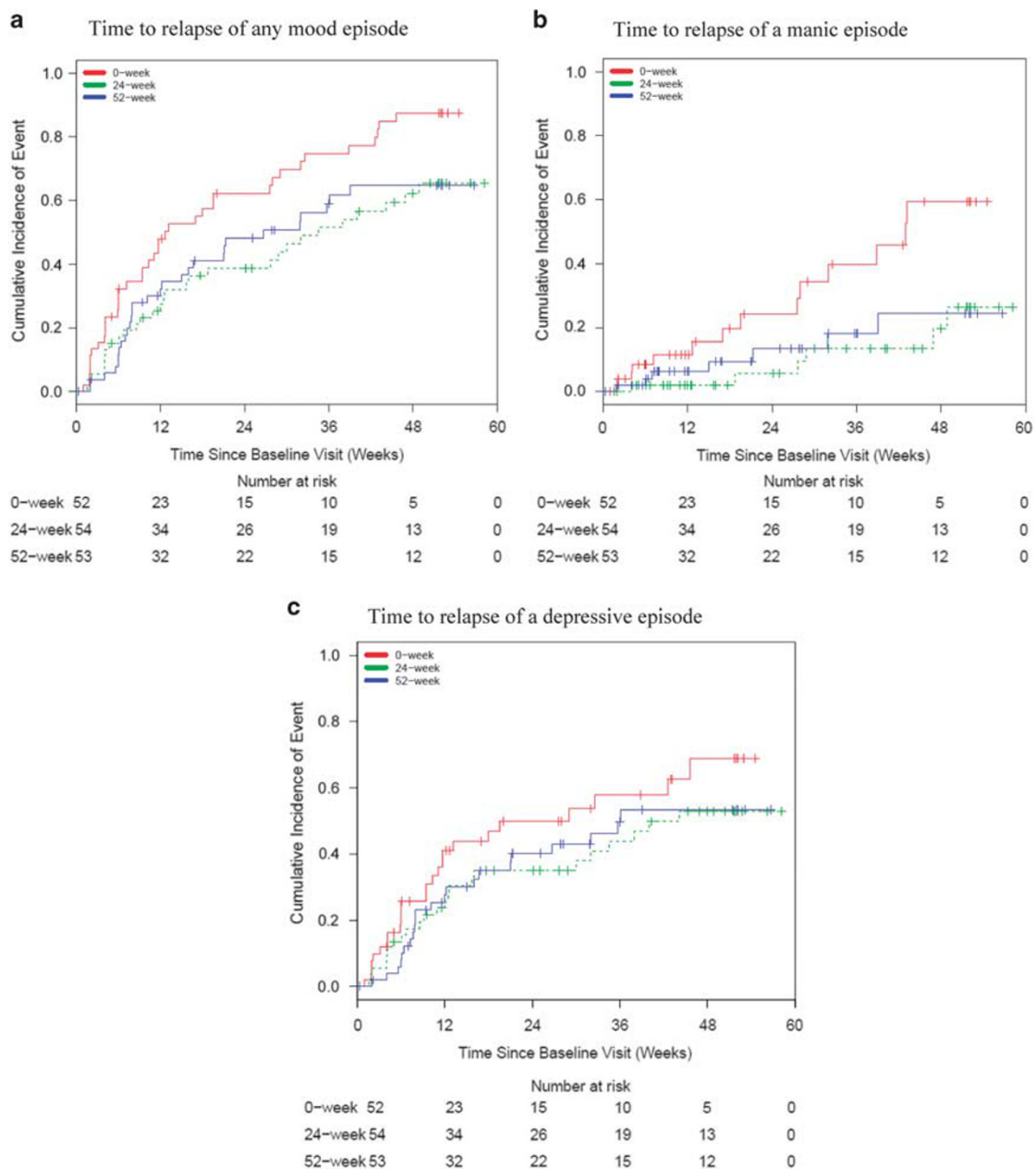
Figure 2. (**a**) Time to relapse of any mood episode. (**b**) Time to relapse of a manic episode. (**c**) Time to relapse of a depressive episode.

therapy for 24 weeks compared with the group that had their atypical antipsychotic discontinued at study entry; (ii) There was a trend for longer time to relapse of any mood episode in the 52-weeks group compared with the 0-weeks group; (iii) The time to relapse of any mood episode was similar in the 52-weeks group compared with the 24-weeks group; however, the sub-group analysis showed discordance in effects of risperidone and olanzapine beyond 24 weeks. In addition, weight gain was significantly greater and more patients gained ⩾ 7% body weight with 52 weeks of continued antipsychotic use compared with 24 weeks.

The findings of this study are highly clinically relevant and have immediate transformational value for the management of bipolar disorder. Although adjunctive atypical antipsychotic therapy was beneficial for 24 weeks after the remission of an acute manic episode, the benefits were not readily apparent beyond 24 weeks as overall, there were no differences in relapse rates between the

24-weeks and 52–weeks groups. Importantly, weight gain was significantly more common in the 52-weeks group compared with the other two groups. Thus, these data suggest that adjunctive atypical antipsychotic therapy beyond 24 weeks confers additional adverse event burden without necessarily offering definitive tangible clinical benefit in efficacy.

Although mania is the defining feature of bipolar I disorder, several studies suggest that depressive episodes and symptoms outnumber manic/hypomanic episodes/symptoms by a ratio of 3:1 during the course of bipolar disorder.[18] Consistent with this, more patients in our study had depressive recurrences compared with manic recurrences (70 vs 27 events, respectively). Despite higher depressive recurrences, adjunctive therapy benefit was more apparent in preventing manic recurrences in the 24-weeks (HR: 0.30) and 52-weeks (HR: 0.43) groups compared with the 0-weeks group than for preventing depressive recurrences

Table 3. Adverse events and changes in Extrapyramidal Symptom Rating Scale (ESRS) scores and metabolic parameters

	Treatment group					
	0 weeks		24 weeks		52 weeks	
	N	%	N	%	N	%
Serious adverse events						
Death	0	0	0	0	1	2
Non-serious adverse events						
Cold/cold Symptoms	5	10	6	11	7	13
Headache	9	17	3	6	6	11
Weight gain	4	8	6	11	7	13
Fatigue/sedation/sleep change	4	8	5	9	4	8
Muscle related injuries	4	8	3	6	5	9
Constipation	3	6	5	9	1	2
Menstrual irregularity/ cramps	2	4	2	4	6	11
Nausea	3	6	4	7	1	2
Diarrhea	1	2	4	7	2	4
Breast changes/ galactorrhea	1	2	3	6	1	2
Dry mouth	2	4	1	2	1	2
Dry skin/itch/rash	1	2	2	4	1	2
Extrapyramidal symptoms	1	2	2	4	1	2
Bloating/flatulence	1	2	1	2	1	2
Dizziness	0	0	2	4	1	2
Hair loss	1	2	0	0	2	4
Impaired sexual function	0	0	3	6	0	0
Elevated glucose	0	0	1	2	1	2
Elevated prolactin level	0	0	1	2	1	2
Impaired vision	0	0	2	4	0	0
Increased appetite	0	0	1	2	1	2
Elevated lipids	0	0	1	2	0	0
Elevated liver function test	0	0	1	2	0	0
Increased dreaming	0	0	1	2	0	0
Tardive dyskinesia	1	2	0	0	0	0
Other	6	12	3	6	3	6
Change from baseline to last visit	Mean	s.d.	Mean	s.d.	Mean	s.d.
ESRS score						
Total	1.3	8.9	2.3	8.3	2.3	9.8
Parkinsonism+Dystonia subscale	− 0.7	3.2	− 0.2	1.8	0.0	4.2
Dyskinesia subscale	0.02	0.32	0.00	0.00	0.02	0.14
Metabolic parameters						
Weight (kg)[a]	− 0.2	4.8	− 0.1	6.8	3.2	6.8
Glucose level (mmol l⁻¹)	0.7	3.7	− 0.01	0.7	0.1	0.9
Cholesterol level (mmol l⁻¹)	− 0.2	1	− 0.3	0.7	0.02	1.0
Triglycerides (mmol l⁻¹)	0.3	1.6	−0.02	0.7	0.1	1.8

Abbreviation: s.d., standard deviation. [a]P-value = 0.01 for the difference between the 52-weeks and 0-weeks groups and between the 52-weeks and 24-weeks groups.

depression (Table 2). These findings are broadly consistent with previous studies[21,22] although the lack of effect of olanzapine in preventing mania is surprising. This might be because many of the patients in the olanzapine 0-weeks group had a depressive event, and thus left fewer patients at risk for mania. The HR for the time to any mood episode comparing the 24-weeks group with the 0-weeks group were similar for both olanzapine and risperidone. Hence, the finding of benefit of 24 weeks of therapy appears robust and applicable to both antipsychotics. In contrast, when comparing the 52-weeks group with the 24-weeks group, the results were discordant between the two antipsychotics. In the risperidone subgroup, the risk of relapse increased with a near doubling of the HR. Even if this result is a false signal and continued use of risperidone beyond 24 weeks does not truly increase the risk of relapse, it remains unlikely that any benefit exists. In the olanzapine subgroup, the risk of relapse decreased with the HR roughly halved though not statistically significant. This result could be because of inadequate sample size. However, this reduction in risk of relapse was accompanied by a 20% increase in risk of weight gain by at least 7% and an average weight gain of nearly 6 kg. Given that the weight gain is a predictor of poor clinical outcomes in bipolar disorder,[23,24] the potential clinical benefit of continuing olanzapine beyond 24 weeks needs to be balanced against the risks of weight-gain-associated morbidity and mortality.

The incidence of adverse events was relatively low and few patients dropped out of the study because of adverse events. There were no significant differences in rates of adverse events, metabolic parameters or ESRS scale scores between the three groups. This may be because of the enriched design in which only those patients who responded and tolerated these medications were eligible to enter the trial. Despite such enrichment in design, patients in the 52-weeks group gained considerably more weight and more patients in this group had clinically significant weight gain, and in particular, those who had received olanzapine adjunctive therapy. This suggests that weight gain with olanzapine may continue beyond 24 weeks.

This study has several strengths including the use of a stratified randomized double-blind design, that it recruited 'real world' patients with and without comorbidity, and allowed routine clinical management including psychoeducation and counseling as clinically indicated. However, some limitations must also be considered. First, this study included only risperidone and olanzapine; hence, the findings of this study may not be generalizable to all atypical antipsychotics. Nevertheless, the findings of this study are consistent with other maintenance studies showing that the efficacy in prevention of relapse is most apparent in the first 6 months. Second, owing to recruitment challenges, the final sample size was smaller than originally planned. Larger sample sizes would have yielded more precise assessments of the differences between the 24-weeks and 52-weeks groups in the olanzapine and risperidone subgroups and provided more definitive conclusions as to whether the discordant findings truly reflect a reduced risk of relapse with continued olanzapine use, an increased risk with continued risperidone use, or both. Third, comparisons of adverse event rates and change in outcome measures may be impacted by differences in the average length of follow-up across treatment groups. However, mean follow-up time in the 24-weeks and 52-weeks arms were similar and so do not explain the weight gain differences between these two groups. Last, clinicians were allowed to provide adjunctive psychological treatments as clinically appropriate. Although differences in types and duration of psychological treatments might have contributed to differences in efficacy, this is also a strength of this study in that it mirrored real world clinical practice.

In conclusion, the results of this study suggest that patients with bipolar I disorder who recently remitted from an acute manic

(HR: 0.65 for the 24 weeks group and HR: 0.73 for the 52 weeks group). These data are consistent with the clinical observation and findings from other studies which suggest that many atypical antipsychotics are more effective in preventing manic than depressive recurrences.[8,9,19,20]

This study was not adequately powered for analysis of the antipsychotic subgroups, but several findings warrant discussion. The prophylactic effect of risperidone was apparent only for mania whereas for olanzapine, the benefit was seen mainly in preventing

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episode with adjunctive risperidone or olanzapine therapy are less likely to have a recurrence if these medications are continued for 24 weeks vs discontinuing soon after remission of mania. However, benefits beyond 24 weeks are not apparent; subgroup results suggest continued risperidone use provides no benefit and although it remains unclear whether continued olanzapine use reduces the risk of recurrence, the potential benefit should be weighed against a concomitant increased risk of weight gain. Given the clinical significance of these findings, future studies should use the similar design to examine the applicability of these findings to other atypical antipsychotics that have less metabolic burden liability.

CONFLICT OF INTEREST

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REFERENCES

1 Miller DS, Yatham LN, Lam RW. Comparative efficacy of typical and atypical antipsychotics as add-on therapy to mood stabilizers in the treatment of acute mania. *J Clin Psychiatry* 2001; **62**: 975–980.
2 Tohen M, Zarate CA Jr. Antipsychotic agents and bipolar disorder. *J Clin Psychiatry* 1998; **59**: 138–148.
3 Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M 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 2013. *Bipolar Disord* 2013; **15**: 1–44.
4 Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition--recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2009; **23**: 346–388.
5 Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry* 2013; **14**: 154–219.
6 Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. 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.
7 Suppes T, Vieta E, Liu S, Brecher M, Paulsson B. 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.
8 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**: 133–144.
9 Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 2010; **71**: 130–137.
10 Tohen M, Chengappa KNR, Suppes T, Baker RW, Zarate CA, Bowden CL et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. *Br J Psychiatry* 2004; **184**: 337–345.
11 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) 1994.
12 Spearing MK, Post RM, Leverich GS, Brandt D, Nolen W. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res* 1997; **73**: 159–171.
13 Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978; **133**: 429–435.
14 Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56–62.
15 Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; **134**: 382–389.
16 Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand Suppl* 1987; **33**: 41–100.
17 Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res* 2005; **76**: 247–265.
18 Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002; **59**: 530–537.
19 Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner S, Kusumakar V. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry* 2010; **68**: 156–162.
20 Keck PE Jr., 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**: 626–637.
21 Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. *Eur Neuropsychopharmacol* 2012; **22**: 339–346.
22 Vieta E, Montgomery S, Sulaiman AH, Cordoba R, Huberlant B, Martinez L et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol* 2012; **22**: 825–835.
23 Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder. *Am J Psychiatry* 2003; **160**: 112–117.
24 Wildes JE, Marcus MD, Fagiolini A. Obesity in patients with bipolar disorder: a biopsychosocial-behavioral model. *J Clin Psychiatry* 2006; **67**: 904–915.