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## Atypical Antipsychotics for Bipolar Disorder: Overblown or Blown Over?

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**Objective :** Developments in the pharmacological treatment of bipolar disorder are of much interest, as the chronicity and disability of the disorder become better understood, and as treatment goals have shifted to emphasise early control of illness course and maintenance of euthymia in addition to acute episodic remission. Atypical antipsychotics have emerged as treatment options, and this paper aims to review the evidence for their role in bipolar disorder.

**Methods :** A MEDLINE search was conducted for publications up till October 2006.

**Results :** The search yielded a number of randomised, controlled clinical trials of various atypical antipsychotics as monotherapy or adjunctive therapy in bipolar disorder. The majority of such trials have investigated their efficacy in acute mania, with fewer studies devoted to acute bipolar depression or maintenance treatment. There are no specific trials on mixed states, which have mainly been studied together with bipolar mania. The most robust evidence supports a class effect of atypical agents in the treatment of mania.

**Conclusions :** There are placebo-controlled trials that support the efficacy of olanzapine and quetiapine in bipolar depression, and of olanzapine and aripiprazole as maintenance treatment. There is strong support for the role of atypical antipsychotics in bipolar disorder management despite a relatively narrow literature base, chiefly for the treatment of mania. However, these findings need to be replicated, and further investigation is warranted to clarify their spectrum of efficacy in bipolar disorder.

**KEY WORDS :** Bipolar disorder; Atypical antipsychotics; Mania; Depression; Maintenance; Clinical trials.

### INTRODUCTION

The understanding of bipolar disorder is expanding. It is now believed to be more prevalent than previously considered, with a recent lifetime prevalence estimate of 3.9% for bipolar I and II combined,<sup>1)</sup> and is recognised for its preponderance of depressive and subsyndromal symptoms.<sup>2,3)</sup> The approach towards its treatment has also been refined, in reflection of new information and broadening pharmacological and psychosocial intervention options.

Treatment goals are ideally remission of the index episode and maintenance of euthymia, without inducing polarity switch or aggravating the illness course. Additional goals directed towards optimising function, facilitating psychological development and treating comorbidities are almost invariably required. Pharmacotherapy is an integral component of bipolar disorder management, in conjunction

with psychotherapy, behavioural and social interventions. However, successful control of the illness in its stabilisation and maintenance aspects is frequently unattainable with monotherapy, and combination psychopharmacotherapy is the more common clinical experience. In broad groups, lithium, anticonvulsants, antidepressants and antipsychotics have been the primary agents used in the treatment of bipolar disorder. Whilst lithium has the most established evidence base for its efficacy in both poles of the illness and in both the acute and prophylactic settings,<sup>4)</sup> anticonvulsants and atypical antipsychotics are emerging with promising roles in the treatment matrix, without the controversy over potential destabilising effects that attends the use of antidepressants.<sup>5)</sup> Atypical antipsychotics, in particular, have attracted much recent research to clarify their indications and limitations in bipolar disorder, and are in the process of assuming a distinct position in the pharmacotherapeutic array of this complex disorder.

This paper aims to review the current state of evidence for the role of atypical antipsychotics in the treatment of bipolar disorder, and to discuss the clinical implications of these findings.

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## Methods

A literature search up to October 2006 was conducted using MEDLINE. Keywords entered in various combinations were bipolar disorder, mania, bipolar depression, depression, maintenance, trials, clinical trials, atypical antipsychotics, olanzapine, risperidone, quetiapine, amisulpride, aripiprazole, clozapine, sertindole and ziprasidone. Randomised, controlled trials were selected as the primary source of information, but non-randomised and open-labelled trials were also reviewed.

## Results

Clinical trials have generally studied individual atypical antipsychotics as monotherapy or in combination with mood stabilisers for either the manic or depressive pole of bipolar disorder. The current literature is weighted towards the study of mania, with only a small number of studies devoted to bipolar depression and maintenance treatment.

### Mania

Efficacy of olanzapine, risperidone, quetiapine, aripiprazole and ziprasidone in acute mania has been demonstrated by randomised, placebo-controlled trials (Table 1).<sup>6-21</sup> Whilst some trials have studied only pure mania, others have included mixed states. As a whole, their results suggest that anti-manic efficacy is likely to be a class effect, which is independent of psychosis, with early differentiation of response and no evidence of treatment-emergent depression. Response, as defined in all these studies, refers to a 50% or greater reduction in total baseline Young Mania Rating Scale (YMRS) or Mania Rating Scale (MRS) scores.

### Aripiprazole

Two 3-week, double-blind, randomised, placebo-controlled trials have measured the efficacy of aripiprazole in treating acute manic or mixed episodes of bipolar disorder. Keck *et al.*<sup>8)</sup> reported a significantly greater reduction of YMRS scores from baseline in the aripiprazole-treated group (N=130) compared to the placebo-treated group (N=132) from day 4 onwards. Response rates at endpoint significantly diverged, with 40% for the aripiprazole-treated group and 19% for the placebo-treated group. In a second trial, 137 patients were randomised to aripiprazole and 135 patients to placebo. Aripiprazole was also observed to be superior to placebo from day 4 onwards, and the response rate at endpoint was higher for the aripiprazole-treated group compared to placebo (53% vs 32%,  $p \leq$

0.001). Mean change in YMRS total score at endpoint was  $-12.5$  for aripiprazole-treated and  $-7.2$  for placebo-treated patients ( $p \leq 0.001$ ).<sup>14,22)</sup>

Aripiprazole was compared with haloperidol in acute bipolar mania in a double-blind, randomised controlled trial over 12 weeks. Patients in manic or mixed episodes were randomised to treatment with aripiprazole (N=175) or haloperidol (N=172). The aripiprazole group showed a higher response rate (50.9%) than the placebo group (29.1%) ( $p < 0.001$ ) at the end of 12 weeks, but these results were confounded by the disparate continuation rates of the two groups (50.9% for aripiprazole, 29.1% for haloperidol,  $p < 0.001$ ), which highlight differences in tolerability more strongly than in efficacy.<sup>23)</sup>

### Olanzapine

The efficacy of olanzapine as monotherapy and adjunctive therapy in mania has been established by several placebo-controlled trials. Two such trials, alike in design, were conducted on patients with bipolar disorder in either manic or mixed episode. One study randomised patients to receive olanzapine monotherapy (N=70) or placebo (N=69) over 3 weeks,<sup>19)</sup> and the other study randomised patients to the same treatment arms (N=55 for olanzapine monotherapy, N=60 for placebo) for 4 weeks.<sup>18)</sup> Both trials found significant score reductions on their primary efficacy measure, the YMRS, in the olanzapine groups (mean score reductions of  $-10.3$ <sup>19)</sup> and  $-14.8$ <sup>18)</sup>) compared with placebo ( $-4.9$  and  $-8.1$ , respectively). Response was also significantly higher in those receiving olanzapine, with proportions of 48.6%<sup>19)</sup> and 64.8%,<sup>18)</sup> in comparison with 24.2% and 42.9% for the respective placebo groups. Subgroup analysis of the pooled results of both trials suggests olanzapine to be effective for both mixed and pure mania, independent of patient demographics and the presence or absence of psychosis.<sup>24)</sup>

The adjunctive utility of olanzapine with mood stabilisers for the treatment of mania has been demonstrated by a 6-week, placebo-controlled trial, in which patients with acute mania or mixed episodes who had only partially responded to two weeks of lithium or valproate monotherapy (YMRS total score  $\geq 16$ ), were randomised to adjunctive olanzapine (N=229) or adjunctive placebo (N=115). Adjunctive olanzapine was superior to adjunctive placebo for the treatment of manic and mixed bipolar episodes in this cohort (mean change in YMRS from baseline of  $-13.1$  for adjunctive olanzapine and  $-9.1$  for placebo,  $p=0.003$ ). Among patients with a mixed episode, adjunctive olanzapine was associated with greater reductions in YMRS ( $-12.9$  vs  $-7.5$ ,  $p < 0.001$ ) and Hamilton Depression Rating Scale (HAM-D-21) ( $-10.3$  vs  $-1.6$ ,

$p<0.001$ ), whereas a trend favouring adjunctive olanzapine was observed among patients presenting with pure mania ( $-13.3$  vs  $-10.6$  on YMRS,  $p=0.09$ ).<sup>17)</sup> In a post hoc analysis of this data, the addition of olanzapine was associated with a significantly lower suicidality score on HAMD within one week, compared with the placebo group.<sup>25)</sup>

There have also been double-blind, randomised, controlled trials comparing olanzapine with other treatments. In a 12-week trial, patients with bipolar mania were ran-

domised to olanzapine ( $N=234$ ) or haloperidol ( $N=219$ ). Both drugs were associated with comparable remission rates ( $52.1\%$  vs  $46.1\%$ ,  $p=0.15$ ), but depressive switch occurred significantly more rapidly in the haloperidol compared to the olanzapine group.<sup>26)</sup> In the same trial, a significantly greater improvement in health-related quality of life and work status was observed for the olanzapine group compared to haloperidol.<sup>27)</sup> This work functional advantage was again observed in a 6-month, open-label extension of the trial.<sup>28)</sup> Compared with lithium, olanzapine

**Table 1.** Randomised, placebo-controlled trials of atypical antipsychotics used as monotherapy or adjunctive therapy in acute mania

Trial	Treatment arms	Numbers in ITT analysis (N)	Duration in weeks	Response (% of patients with ≥50% reduction in YMRS score)	Mean change in YMRS from baseline
Monotherapy					
Keck et al <sup>8)</sup>	Aripiprazole	123	3	40 <sup>c</sup>	−8.2 <sup>c</sup>
	Placebo	122		19	−3.4
Sachs et al <sup>14)</sup>	Aripiprazole	136	3	53 <sup>d</sup>	−12.5 <sup>d</sup>
	Placebo	132		32	−7.2
Tohen et al <sup>19)</sup>	Olanzapine	70	3	48.6 <sup>c</sup>	−10.3 <sup>a</sup>
	Placebo	69		24.2	−4.9
Tohen et al <sup>18)</sup>	Olanzapine	54	4	65 <sup>a</sup>	−14.8 <sup>d</sup>
	Placebo	56		43	−8.1
McIntyre et al <sup>11)</sup>	Quetiapine	101	3	42.6	−12.3 <sup>b</sup>
	Haloperidol	98		56.1 <sup>b</sup>	−15.7 <sup>d</sup>
	Placebo	100		35.0	−8.3
Bowden et al <sup>6)</sup>	Quetiapine	107	3	53.3 <sup>d</sup>	−14.6 <sup>d</sup>
	Lithium	98		53.1 <sup>d</sup>	−15.2 <sup>d</sup>
	Placebo	95		27.4	−6.7
Hirschfeld et al <sup>7)</sup>	Risperidone	127	3	43 <sup>b</sup>	−10.6 <sup>d</sup>
	Placebo	119		24	−4.8
Khanna et al <sup>10)</sup>	Risperidone	146	3	73 <sup>d</sup>	−22.7 <sup>d</sup>
	Placebo	144		36	−10.5
Smulevich et al <sup>16)</sup>	Risperidone	153	3	48 <sup>b</sup>	−15.1 <sup>d</sup>
	Haloperidol	144		47	−13.9 <sup>d</sup>
	Placebo	138		33	−9.4
Keck et al <sup>9)</sup>	Ziprasidone	131	3	n/a	−12.4 <sup>c*</sup>
	Placebo	66		n/a	−7.8
Potkin et al <sup>12)</sup>	Ziprasidone	137	3	46 <sup>a</sup>	−11.1 <sup>b*</sup>
	Placebo	65		29	−5.6
Adjunctive therapy					
Tohen et al <sup>17)</sup>	Olanzapine	220	6	67.7 <sup>d</sup>	−13.1 <sup>c</sup>
	Placebo	114		44.7	−9.1
Sachs et al <sup>13)</sup>	Quetiapine	81	3	54.3 <sup>c</sup>	−13.8 <sup>a</sup>
	Placebo	89		32.6	−9.9
Yatham et al <sup>21,32)</sup>	Quetiapine	185	3	55.7 <sup>b</sup>	−15.3 <sup>a</sup>
	Placebo	185		41.6	−12.2
Sachs et al <sup>15)</sup>	Risperidone	51	3	n/a	−14.3 <sup>b</sup>
	Haloperidol	50		n/a	−13.4 <sup>a</sup>
	Placebo	47		n/a	−8.2
Yatham et al <sup>20)</sup>	Risperidone	69	3	59 <sup>a</sup>	−14.5
	Placebo	73		41	−10.3

ITT, Intent-to-treat; YMRS, Young Mania Rating Scale; n/a, Not available, <sup>a</sup> $p<0.05$  compared with placebo, <sup>b</sup> $p<0.01$  compared with placebo, <sup>c</sup> $p\leq 0.005$  compared with placebo, <sup>d</sup> $p\leq 0.001$  compared with placebo, \*Mania Rating Scale (MRS) used

was at least equally effective in the treatment of acute mania in a 4-week trial where patients were randomised to either olanzapine (N=15) or lithium (N=15).<sup>29)</sup> Olanzapine was superior to divalproex in a 3-week study of hospitalised patients with acute bipolar manic or mixed episodes, who were randomised to olanzapine (N=125) or divalproex (N=123). At endpoint, mean reduction in YMRS scores was 13.4 for the olanzapine group and 10.4 for the divalproex group ( $p<0.03$ ). Response was seen in 54.4% of olanzapine treated patients and in 42.3% of divalproex treated patients ( $p=0.058$ ).<sup>30)</sup>

In a trial of a first episode population, 77 individuals between the age of 15 and 28 years were randomised to either a combination of olanzapine and lithium or chlorpromazine and lithium in the treatment of a first manic episode. The duration of the acute phase of the trial was 8 weeks, and there was an 18 month follow up period. They were randomised to either olanzapine, started at 5 mg per day, or chlorpromazine, started at 100 mg per day, with doses titrated according to need. All individuals were on concurrent treatment with lithium, serum levels between 0.8 and 1.0. There was a significant advantage of olanzapine over chlorpromazine at the end of the 8 week acute phase of the trial on the YMRS at weeks 4 ( $p=0.016$ ) and 8 ( $p=0.082$ ; Kruskal Wallis test). There was a similar advantage for olanzapine on the BPRS, SAPS and SANS at the end of 4 weeks of treatment. Discontinuation rates did not differ between the two groups.<sup>31)</sup>

#### Quetiapine

Two placebo-controlled trials of quetiapine monotherapy have been conducted for the treatment of acute mania. They had similar protocols, which entailed double-blind randomisation of bipolar I disorder patients in a manic episode to three monotherapy treatment arms over 12 weeks, with change in YMRS score from baseline serving as the primary outcome measure. In the first study, patients were randomised to quetiapine (N=102), haloperidol (N=99) and placebo (N=101). The quetiapine group showed a significant advantage over placebo after 3 weeks (mean YMRS score reduction of  $-12.3$  vs  $-8.3$ ,  $p<0.01$ ). At the end of 12 weeks, quetiapine was superior to placebo ( $-17.5$  vs  $-9.5$ ,  $p<0.001$ ), and had similar efficacy as haloperidol.<sup>11)</sup> The second study randomised patients to quetiapine (N=107), lithium (N=98) and placebo (N=97). Quetiapine was superior to placebo at the end of 3 weeks (mean YMRS score reduction of  $-14.6$  vs  $-6.7$ ,  $p<0.001$ ) and 12 weeks ( $-20.8$  vs  $-9.0$ ,  $p<0.001$ ), and was comparable in efficacy with lithium.<sup>6)</sup> Analysis of the pooled data from both studies indicated significant differentiation of the efficacy of quetiapine over placebo from

Day 4 until the end of 12 weeks.<sup>32)</sup>

The efficacy of quetiapine as adjunctive treatment with mood stabilisers was demonstrated in two 3-week, double-blind, parallel group trials of bipolar I disorder patients in a manic episode. The patients, who were already on either lithium or divalproex, were randomised to quetiapine or placebo. In the first study, reduction in YMRS scores from baseline at 3 weeks was significantly greater for the quetiapine-treated (N=91) than the placebo-treated (N=100) patients ( $-13.8$  vs  $-9.9$ ,  $p=0.021$ ). Response and remission rates, the latter defined as YMRS score of less than 12, were also significantly higher for quetiapine compared with placebo ( $54.3\%$  vs  $32.6\%$ ,  $p=0.005$  and  $45.7\%$  vs  $25.8\%$ ,  $p=0.007$ ).<sup>13)</sup> Data from this study were pooled with a second trial, conducted under identical protocols with the exception of a longer double-blind follow-up period of 6 weeks, which showed non-significant trends in favour of quetiapine.<sup>21,33)</sup> The combined data demonstrated superiority of quetiapine over placebo after one week of treatment, which remained significant at the end of 3 weeks, as measured by mean YMRS score reduction ( $-15.3$  vs  $-12.2$ ,  $p<0.05$ ). Response rate was greater in the quetiapine-treated patients ( $55.7\%$  vs  $41.6\%$ ,  $p<0.01$ ) at end-point.

#### Risperidone

The efficacy of risperidone monotherapy over placebo in the treatment of acute mania has been observed in three randomised, double-blind, placebo-controlled trials. Hirschfeld *et al.*<sup>7)</sup> found significantly greater improvement in mean YMRS score in their risperidone-treated patients with pure mania (N=125) compared with placebo-treated patients (N=134) as early as 3 days after treatment, and this significant difference increased at the 3-week endpoint ( $-10.6$  vs  $-4.8$ ,  $p<0.001$ ). Efficacy of onset early and comparable magnitude was also reported by Khanna *et al.*<sup>10)</sup> In their cohort of bipolar I patients presenting with a manic or mixed episode, those randomised to risperidone monotherapy (N=146) showed significantly greater improvement than placebo-treated patients in mean YMRS score reduction from Week 1 until trial completion at Week 3 ( $-22.7$  vs  $-10.5$  at end-point,  $p<0.001$ ). The superiority of risperidone was significant for both pure and mixed mania, and for those with and without psychotic features. A 9-week, open-label extension trial was conducted for patients who completed these two double-blind trials, and found further significant improvements for both those who continued or switched to risperidone.<sup>34)</sup> A third study randomised patients with bipolar mania to risperidone (N=154), haloperidol (N=144) and placebo (N=140) monotherapy for 3 weeks, which was followed by a 9-week

double-blind phase comparing risperidone with haloperidol. At the end of the first 3-week phase, mean YMRS score reductions were significantly greater for the risperidone group compared with placebo ( $-15.1$  vs  $-9.4$ ,  $p<0.001$ ), but differences between risperidone and haloperidol were non-significant. In the 9-week continuation phase, both treatment groups showed further mean reductions in YMRS scores from baseline ( $-28.7$  for risperidone and  $-27.3$  for haloperidol).<sup>16)</sup>

In a 4-week, double-blind, randomised controlled trial comparing risperidone ( $N=15$ ), lithium ( $N=15$ ) and haloperidol ( $N=15$ ) in hospitalised patients with acute mania, risperidone showed equivalent efficacy as lithium and haloperidol.<sup>35)</sup> Extrapyramidal side effects from risperidone were noted to occur as commonly as haloperidol in this study, when a fixed dose of 6 mg per day of risperidone was used. However, this was less frequently encountered in risperidone-treated than haloperidol-treated patients when lower doses were used.<sup>16)</sup>

The utility of risperidone as adjunctive treatment with mood stabilisers for acute mania has support from open-labelled studies,<sup>36-39)</sup> and has been further substantiated by double-blind, randomised, placebo-controlled trials. In one study, bipolar patients in manic or mixed episodes who were treated with lithium or divalproex, were randomised to receive adjunctive risperidone ( $N=52$ ), haloperidol ( $N=53$ ) or placebo ( $N=51$ ) for 3 weeks. Significant improvements from baseline YMRS scores were observed at end-point for patients receiving adjunctive risperidone and haloperidol compared to those receiving lithium or divalproex alone (mean reductions on YMRS of  $-14.3$ ,  $-13.4$  and  $-8.2$ , respectively).<sup>15)</sup> In an open-labelled, 10-week continuation phase of this study, patients were treated with risperidone in conjunction with a mood stabiliser. Significant further improvement was observed for the cohort, which showed a remission rate of 79% at the end of the trial, with remission defined as  $YMRS \leq 12$ .<sup>40)</sup> A second placebo-controlled study randomised patients with manic or mixed episodes to adjunctive treatment over 3 weeks with risperidone ( $N=75$ ) or placebo ( $N=75$ ), in addition to treatment with lithium, divalproex or carbamazepine. A non-significantly greater mean YMRS score reduction was found at end-point for the risperidone group compared with placebo ( $-14.5$  vs  $-10.3$ ), although the response rate was significantly greater for the risperidone group (59% vs 41%,  $p<0.05$ ). It was notable that risperidone plasma concentrations were 40% lower in the subgroup receiving carbamazepine, and the differences in primary outcome measures reached significance in favour of the risperidone group when carbamazepine-treated patients were excluded from analysis.<sup>20)</sup>

### Ziprasidone

Ziprasidone monotherapy in bipolar mania was investigated by two 3-week, double-blind, randomised, placebo-controlled trials of similar designs. In the earlier trial, patients with bipolar I disorder in manic or mixed episodes were randomised to ziprasidone ( $N=140$ ) or placebo ( $N=70$ ). Improvement, as measured by reduction in Mania Rating Scale (MRS) scores, was observed within 2 days and was significantly greater in ziprasidone-treated than placebo-treated patients at end-point (mean MRS score reduction was  $-12.4$  vs  $-7.8$ ,  $p<0.005$ ).<sup>9)</sup> The subsequent trial had sample sizes of 137 patients in the ziprasidone and 65 patients in the placebo groups. Similar efficacy of ziprasidone from Day 2 until end-point was reported (mean score reduction on MRS at end-point was  $-11.1$  for ziprasidone and  $-5.6$  for placebo,  $p<0.01$ ).<sup>12)</sup>

One randomised, placebo-controlled trial studied the adjunctive efficacy of ziprasidone. In this 3-week trial, hospitalised patients with bipolar mania received either adjunctive ziprasidone ( $N=102$ ) or placebo ( $N=103$ ), in addition to treatment with lithium. Although significantly greater improvement was seen in ziprasidone-treated patients at day 4, improvements were not significantly different between the two groups at endpoint.<sup>41)</sup>

### Amisulpride and Clozapine

No randomised, controlled data were available for the efficacy of amisulpride and clozapine in mania, but open-labelled trials have been conducted.

In a small, open-labelled, 6-week study comprising of 20 patients with bipolar mania, amisulpride was administered but established mood stabilisers were allowed to be continued without dose alterations. Significant improvement was found as measured using the YMRS, HAMD and the Clinical Global Impressions Scale for Bipolar Disorder, Modified (CGI-BP-M).<sup>42)</sup>

The efficacy of clozapine in treating and preventing mania has been supported by case series,<sup>43)</sup> retrospective<sup>44)</sup> and open-labelled studies,<sup>45,46)</sup> which have mostly focussed on treatment-resistant populations. In their prospective, 13-week, open-labelled trial of clozapine monotherapy in 25 patients with treatment-resistant mania, Calabrese *et al.*<sup>45)</sup> reported marked improvement on YMRS, although benefits were differentially in favour of those with a bipolar rather than a schizoaffective disorder diagnosis and those with non-rapid-cycling rather than rapid-cycling course. A 12-week, open-labelled trial of clozapine monotherapy in 22 patients with treatment-resistant bipolar psychotic mania also reported efficacy, with mean improvements of 56.7%, 56.6% and 39.1% on the Brief Psychiatric Rating Scale (BPRS), YMRS and CGI, respectively.<sup>46)</sup> A randomised

mised, open-labelled study investigated adjunctive clozapine (N=19) compared with treatment as usual (N=19) for patients with treatment-resistant schizoaffective or bipolar disorder with a history of mania. After one year, significant differences were found on global, mania, psychotic symptoms and involuntary movement rating scales, but not on HAMD.<sup>47)</sup> Naturalistic studies have also provided support for the utility of clozapine in treatment-resistant bipolar disorder.<sup>48,49)</sup>

### Bipolar Depression

Open-labelled studies have suggested efficacy of olanzapine,<sup>50)</sup> quetiapine<sup>51,52)</sup> and risperidone<sup>50,53)</sup> in bipolar depression, but there are few randomised, controlled trials of atypical antipsychotics in this area (Table 2).

Data are available from two double-blind, randomised, placebo-controlled trials that support the efficacy of olanzapine and quetiapine in the treatment of acute bipolar depression. In their multi-centred, 8-week trial, Tohen *et al.*<sup>54)</sup> recruited patients with bipolar I disorder, depressive episode, who scored at least 20 on the Montgomery-Asberg Depression Rating Scale (MADRS). They were randomised to receive olanzapine (N=370), olanzapine-fluoxetine combination (N=86) or placebo (N=377). From Week 1 onwards, both the olanzapine and olanzapine-fluoxetine combination groups showed significantly greater improvement than the placebo group, and from Week 4 onwards, the olanzapine-fluoxetine combination group was superior to the olanzapine group. At end-point,

the mean reductions from baseline in MADRS scores were -11.9, -15.0 and -18.5 for the placebo, olanzapine and olanzapine-fluoxetine combination, respectively. Response rate, defined as  $\geq 50\%$  reduction in MADRS score, was 30.4% for placebo, 39.0% for olanzapine and 56.1% for olanzapine-fluoxetine. Remission, defined as a MADRS score  $\leq 12$  at end-point, was achieved by 24.5%, 32.8% and 48.8% of the respective groups. Times to response and remission were shortest for the olanzapine-fluoxetine combination, followed by olanzapine then placebo. Adverse effects of the active treatments were similar, except for higher rates of nausea and diarrhoea for the olanzapine-fluoxetine combination. Of particular interest, treatment-emergent mania did not differ among the three groups during the 8-week period. In the 6-month, open-label extension to this trial, patients were continued on either olanzapine, the olanzapine-fluoxetine combination, or were switched from one to the other. Among those who had not entered remission, the majority achieved remission during the extension trial, and those who had already remitted maintained their MADRS scores at end-point, with the exception of the switch group, which showed an increase of 2.3 ( $p=0.02$ ).<sup>55)</sup>

In the BOLDER I study, Calabrese *et al.*<sup>56)</sup> conducted an 8-week, randomised, placebo-controlled trial of quetiapine in patients with bipolar I (N=360) or bipolar II (N=182) disorder who were in a major depressive episode. The patients were randomly allocated to receive quetiapine at 300 mg daily dose (N=172), 600 mg daily

**Table 2.** Randomised, controlled trials of atypical antipsychotics in bipolar depression

Trial	Treatment arms	Numbers in ITT analysis (N)	Duration in weeks	Response (% of patients with ≥ 50% reduction in MADRS score)	Mean change in MADRS from baseline
Placebo-controlled					
Tohen et al <sup>[54]</sup>	Olanzapine	351	8	39.0 <sup>a</sup>	−15.0 <sup>b</sup>
	Olanzapine/fluoxetine	82		56.1 <sup>b</sup>	−18.6 <sup>b</sup>
	Placebo	355		30.4	−11.9
Calabrese et al <sup>[56]</sup>	Quetiapine 300 mg	172	8	57.6 <sup>b</sup>	−16.4 <sup>b</sup>
	Quetiapine 600 mg	170		58.2 <sup>b</sup>	−16.7 <sup>b</sup>
	Placebo	169		36.1	−8.5
Amsterdam and Shults <sup>[59]</sup>	Fluoxetine	8	8	n/a	n/a
	Olanzapine	8		n/a	n/a
	Olanzapine/fluoxetine	9		n/a	n/a
	Placebo	9		n/a	n/a
Non-placebo-controlled					
Brown et al <sup>[60]</sup>	Olanzapine/fluoxetine	205	7	68.8	−14.9 <sup>c</sup>
	Lamotrigine	205		59.7	−12.9
Shelton and Stahl <sup>[61]</sup>	Adjunctive (to mood stabiliser) :		12		
	Risperidone	10		n/a	−4.2
	Paroxetine	10		n/a	−7.9
	Risperidone/paroxetine	10		n/a	−5.8

ITT, Intent-to-treat; MADRS, Montgomery-Asberg Depression Rating Scale; n/a, Not available, <sup>a</sup> $p < 0.05$  compared with placebo, <sup>b</sup> $p \leq 0.001$  compared with placebo, <sup>c</sup> $p = 0.002$  between comparators

dose (N=170), or placebo (N=169). Both quetiapine groups were superior to placebo from Week 1 onwards, and mean reductions in MADRS scores at end-point were -10.3 for placebo, -16.4 for quetiapine 300 mg/day, and -16.7 for quetiapine 600 mg/day. Response rates for both quetiapine groups were similar (57.6% for 300 mg/day and 58.2% for 600 mg/day), and significantly greater than placebo (36.1%,  $p<0.001$ ), although significant differentiation of responders was observed earlier (Week 1) for those receiving 600 mg/day quetiapine than those on 300 mg/day (Week 2). The quetiapine groups shared the same remission rate (52.9%), which was significantly higher than placebo (28.4%) ( $p<0.001$ ). Quetiapine was well-tolerated, and treatment-emergent mania rates did not significantly differ between the quetiapine and placebo groups (3.2% and 3.9%, respectively). The effect size was 0.81 for 600 mg/day quetiapine and 0.67 for 300 mg/day quetiapine. In the bipolar I subgroup, effect sizes were 1.09 for the 600 mg/day group and 0.91 for the 300 mg/day group, whereas the corresponding figures were 0.39 and 0.28 in the bipolar II subgroup. These figures compared with an effect size of 0.31 for the olanzapine monotherapy trial.<sup>54)</sup> Secondary analysis of data from this trial also found significant anxiety reduction associated with quetiapine monotherapy in the bipolar I subgroup.<sup>57)</sup> Efficacious results of quetiapine monotherapy have been replicated in the recently completed 8-week, double-blind BOLDER II study (N=509), which reported significant end-point mean MADRS reductions for both the 300 mg/day and 600 mg/day dosages of quetiapine, with respective effect sizes of 0.61 and 0.54, and no differentiation of efficacy between the two dosages.<sup>58)</sup>

A small placebo-controlled trial of olanzapine, fluoxetine and the olanzapine-fluoxetine combination was conducted in 30 bipolar I or bipolar II disorder patients in a major depressive episode. Significant improvements were observed in all comparison groups, but no significant differences were found among them. However, conclusions could not be confidently derived as the study was inadequately powered to detect statistical differences in efficacy.<sup>59)</sup>

Brown *et al.*<sup>60)</sup> compared the olanzapine-fluoxetine combination with lamotrigine in a 7-week double-blind, randomised, controlled trial which recruited patients with a diagnosis of bipolar I disorder, depressed. Although patients treated with the olanzapine-fluoxetine combination (N=205) demonstrated significantly greater improvement than those treated with lamotrigine (N=205) on the CGI, MADRS and YMRS, the effect sizes were small. Response rates were similar between the two groups, but the olanzapine-fluoxetine combination group had a shorter

time to response. Adverse effects were more common for the olanzapine-fluoxetine combination, but suicidal and self-injurious behaviour occurred more frequently in the lamotrigine group. The lack of placebo control and the 5-week titration period for lamotrigine were two factors that limited the interpretation of these results.

The adjunctive role of atypical antipsychotics has been investigated. A small, 12-week, double-blind, randomised, controlled trial compared risperidone, paroxetine and the combination of both in patients with a depressive phase of bipolar I or II disorder, who were already established on a mood stabiliser. They were assigned to treatment with risperidone plus placebo, paroxetine plus placebo, and risperidone plus paroxetine (N=10 for all groups). All groups showed modest but significant improvement, although they did not differentiate from one another in outcome.<sup>61)</sup> In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, 66 patients with treatment-resistant bipolar depression, as defined by non-response to a combination of mood stabilisers plus at least one antidepressant, were randomised to open-label adjunctive treatment with lamotrigine, inositol or risperidone. At the end of 16 weeks, the groups did not significantly differ in their rates of recovery, but the lamotrigine group had lower depression, global and functional ratings than the other groups.<sup>62)</sup>

### Maintenance

A limited number of randomised, controlled trials has investigated aripiprazole monotherapy, olanzapine monotherapy and olanzapine adjunctive to a mood stabiliser as maintenance pharmacotherapy in bipolar disorder (Table 3).

The prophylactic efficacy of olanzapine was demonstrated in a study, in which patients with bipolar I disorder who had remitted from a manic or mixed episode with open-label olanzapine monotherapy were randomised to receive maintenance olanzapine (N=255) or placebo (N=136) for up to 48 weeks. Using a YMRS or HAMD score  $\geq 15$  or hospitalisation as markers of symptomatic relapse, those assigned to olanzapine had a significantly lower relapse rate than those assigned to placebo (46.7% vs 80.1%,  $p<0.001$ ), which corresponded to a number needed to treat of 3.0 (95% confidence interval 2.3–4.1). The median time to symptomatic relapse into a subsequent mood episode was significantly longer for the olanzapine than the placebo group (174 days vs 22 days,  $p<0.001$ ). This advantage appeared to apply to manic, depressive and mixed episodes.<sup>63,64)</sup>

Olanzapine was compared with lithium in a 12-month trial, which recruited patients initially presenting with ei-



**Table 3.** Randomised, controlled trials of atypical antipsychotics as maintenance treatment in bipolar disorder

Trial	Treatment arms	Numbers in ITT analysis (N)	Duration	Median time to symptomatic relapse in days	Rate of symptomatic relapse (%)
<b>Placebo-controlled</b>					
Keck et al <sup>71)</sup>	Aripiprazole	77	26 weeks	n/a	n/a
	Placebo	83		n/a	n/a
Tohen et al <sup>63)64)</sup>	Olanzapine	225	48 weeks	174 <sup>a</sup>	46.7 <sup>a</sup>
	Placebo	136		22	80.1
Tohen et al <sup>70)</sup>	Adjunctive (to lithium or valproate):				
	Olanzapine	51	18 months	163 <sup>b</sup>	37 <sup>c</sup>
	Placebo	48		42	55
<b>Non-placebo-controlled</b>					
Tohen et al <sup>68)</sup>	Olanzapine	125	47 weeks	NS	42.4 <sup>c</sup>
	Divalproex	126			56.5
Tohen et al <sup>65,66)</sup>	Olanzapine	217	12 months	NS	30.0 <sup>d</sup>
	Lithium	214			38.8

ITT, Intent-to-treat; n/a, Not available; NS, Non-significant difference, <sup>a</sup>p<0.001 between comparators, <sup>b</sup>p=0.023, <sup>c</sup>Non-significant, <sup>d</sup>p=0.055

ther a manic or mixed episode that subsequently remitted on open-label olanzapine and lithium. They were then randomised to double-blind olanzapine (N=217) or lithium (N=214) monotherapy. Symptomatic relapse rates were not significantly different between the two groups (30.0% for olanzapine and 38.8% for lithium). However, olanzapine was superior to lithium in preventing manic or mixed episode relapse, and the two agents were comparable in preventing depressive relapse.<sup>65,66)</sup> Post hoc analysis of data from this study reported significantly lower manic or mixed, but not depressive, relapses with olanzapine for those classified as having early-stage (ie 2 prior manic/mixed episodes) bipolar disorder.<sup>67)</sup> Comparison data with divalproex is also available from a 47-week double-blind trial of bipolar patients who presented with a manic or mixed episode. Olanzapine-treated patients (N=125) remitted earlier than divalproex-treated patients (N=126) (median time to remission 14 days vs 62 days, p<0.05) and had a greater mean reduction in YMRS score at end-point (-15.4 vs -12.5, p=0.03), although the remission rates of the groups did not significantly differ. Neither the recurrence rates for an affective episode nor the time to recurrence was significantly different between the olanzapine and divalproex groups.<sup>68)</sup> A post hoc analysis of this trial suggested that olanzapine and divalproex had similar anti-manic efficacy for both rapid and non-rapid cycling patients, but olanzapine was superior to divalproex for non-rapid cycling patients.<sup>69)</sup>

An 18-month, double-blind, placebo-controlled trial investigated the adjunctive benefits of olanzapine as bipolar maintenance treatment. This was an extension to a previously cited trial of adjunctive olanzapine in acute mania,<sup>17)</sup> and included patients who achieved remission with olanzapine plus either lithium or valproate. They were

randomly assigned to treatment with olanzapine plus lithium or valproate (N=51), or placebo plus lithium or valproate (N=48). Time to syndromic relapse (when patients met diagnostic criteria for a manic, mixed or depressive episode) was not significantly different for the two groups. However, when the less stringent criteria of symptomatic relapse (defined as a YMRS or HAMD-21 score ≥15) were used, the olanzapine-treated group had a significantly longer time to relapse into a subsequent affective episode, but relapse rates did not significantly differ.<sup>70)</sup> Weight gain was a consistent significant treatment-emergent event associated with olanzapine that was reported by all the above longitudinal trials.<sup>63-66,68,70)</sup>

A single double-blind trial of aripiprazole was conducted in recently manic patients with bipolar I disorder. Patients who had been stabilised on open-label aripiprazole were randomised to aripiprazole (N=78) or placebo (N=83) for 26 weeks. The aripiprazole patients had fewer affective relapses than the placebo patients (25% vs 43%, p=0.013), and showed a significantly delayed time to relapse. However, the delay of relapse was only significant for manic but not depressive relapses.<sup>71,72)</sup>

A small open-labelled study has suggested that amisulpride may be useful in reducing manic relapse.<sup>73)</sup>

### Mixed States

The concept of mixed states is still being refined, and various definitions are available, including that of concurrent diagnostic criteria for both major depressive episode and mania as stipulated by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR),<sup>74)</sup> and those with less stringent criteria that focus on the predominant affective state.<sup>75,76)</sup> In studies of atypical antipsychotic treatment in bipolar disorder, mixed states have mostly

been defined using DSM-IV-TR criteria and included with mania. Results from these studies have generally supported the efficacy of atypical antipsychotics for the acute and maintenance treatment of the manic and mixed episode cohorts,<sup>8-10,12,15,17-19,30,40</sup> but no trial has specifically investigated those with mixed states. In a pooled data analysis of two placebo-controlled trials of olanzapine in acute mania, efficacy was found to be comparable between the pure mania and mixed episode subgroups.<sup>24</sup> However, in a placebo-controlled trial comparing the olanzapine plus mood stabiliser combination with mood stabiliser monotherapy, cotherapy with olanzapine was associated with greater benefits for mixed than pure mania.<sup>17</sup>

### Bipolar Disorder in Children and Adolescents

Trials of atypical antipsychotics in paediatric and adolescent bipolar disorder are few in number and have small sample sizes. The efficacy of olanzapine monotherapy,<sup>77,78</sup> risperidone monotherapy<sup>78</sup> and adjunctive risperidone<sup>79</sup> in bipolar mania has been supported by open-labelled studies.

The use of quetiapine in adolescent mania has been studied in two double-blind, randomised, controlled trials. In comparison with divalproex, quetiapine showed similar reduction in YMRS scores in a 28-day study of 50 patients, but was associated with more rapid improvement and greater response and remission rates.<sup>80</sup> When initiated at the same time as divalproex in a 6-week trial on 30 patients, the quetiapine-divalproex combination demonstrated significantly greater score reduction from baseline on YMRS and a higher response rate (83% vs 53%,  $p=0.05$ ) than divalproex monotherapy.<sup>81</sup>

## Discussion

The pharmacotherapy of bipolar disorder has increased in complexity, as treatment goals have become more precise and involve not only acute episodic remission, but the prevention of subsequent episodes and tempering of potentially aggressive illness course. Clinically, combination therapy frequently appears necessary in addressing these goals, as pharmacological agents seem differentially efficacious for distinct poles and phases of the illness. For atypical antipsychotics, there is strong support for their role in bipolar disorder management despite a relatively narrow literature base. However, their inter- and intra-class comparative efficacies for each illness pole or phase await further delineation.

There is convincing evidence of efficacy for atypical antipsychotics in the treatment of acute mania. As a class, they have demonstrated anti-manic properties that are inde-

pendent of psychosis, and have been associated with early improvements, often within days. For olanzapine and quetiapine, their efficacy in mania has been comparable to lithium in individual trials. The adjunctive benefits of olanzapine, risperidone and perhaps quetiapine have been suggested by randomised controlled trials. The tolerability of atypical antipsychotics has generally been favourable in clinical trials, although the consistent reports of weight gain from olanzapine present concerns for its use as maintenance therapy.

In bipolar depression, fewer studies of atypical antipsychotics are available, and results in favour of their use have been less consistent. However, there is one placebo-controlled trial for olanzapine and two for quetiapine that demonstrated their efficacy. The differential effect sizes for the quetiapine and olanzapine monotherapy data sets are intriguing. If this reflects trial selection differences, the variable outcomes seen in many trials of agents in a single class across multiple trials or a true difference in efficacy remains uncertain. Head to head trials are needed to answer this more definitively.

No increase in manic switch was reported, although the trial periods were only eight weeks in duration. Notably, the olanzapine-fluoxetine combination was superior to olanzapine in acute bipolar depression during the acute 8-week study, but greater improvement was observed for olanzapine than the olanzapine-fluoxetine combination in the 24-week extension study, without apparent dissimilarities in manic switch rates. This raises the possibility that combination therapy may produce a synergistic effect in the short-term, but its long-term improvement trajectory may not substantially differ from olanzapine monotherapy.

In maintenance phase, the existing limited evidence supports the prophylactic efficacy of olanzapine for manic, mixed and depressive relapses. It may be superior to lithium for manic or mixed relapses, and may be superior to divalproex in non-rapid cycling patients. These findings require replication. There is one trial supporting the utility of aripiprazole in manic but not depressive prophylaxis, but the generalisability of such maintenance benefits to other agents in the class awaits further clinical trials.

The current evidence best supports atypical antipsychotics as anti-manic agents, but the extent of their mood stabilising potential is yet to be fully clarified. The clinical implications of such findings are significant, as alternative treatment options for bipolar disorder are either equally restricted in evidence base, as in the case of some novel anticonvulsants, or are associated with substantial side effects. Therefore, the availability of efficacious yet well-tolerated options is an important treatment advance. Furthermore, the treatment of bipolar subgroups, such as

the first episode, dual diagnosis, mixed states and rapid cycling illness, are relatively unexplored and the ability of atypical antipsychotics to contribute in these specific areas may warrant closer investigation. These agents may also have a distinct anxiety-reducing profile, as suggested by a quetiapine trial, and may prove to be an additional benefit in the treatment of bipolar disorder.

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