

REVIEW

OPEN ACCESS

Full open access to this and thousands of other papers at <http://www.la-press.com>.

Pharmacotherapy Update: Quetiapine use in Bipolar Disorder—What does the evidence tell us?

Mark Taylor¹, Kirsty Mackay¹ and Polash Shajahan²

¹Ballenden House, Edinburgh EH8 9HL, UK. ²Bellshill Clinic, Bellshill, Lanarkshire ML4 1PS, UK.
Email: marktaylor2@nhs.net

Abstract: Bipolar disorder is a common and serious illness usually requiring long term medication. We critically review the available evidence surrounding the increasing use of quetiapine, a second generation antipsychotic, in both the acute and maintenance phases of bipolar disorder. Large scale, randomized controlled data supports the use of quetiapine in both acute mania and acute bipolar depression, as a safe and effective treatment and probably best used in combination with a traditional ‘mood stabiliser’ such as lithium or divalproex. Also, quetiapine monotherapy has been shown to be effective in bipolar depression. Two recently published studies also confirm that quetiapine in combination with either lithium or divalproex ‘adds value’ to the maintenance treatment of bipolar disorder in terms of delaying relapse compared to either lithium or divalproex alone. Quetiapine is generally well tolerated, although further work on long term weight gain and emergent diabetes would be helpful.

Keywords: quetiapine, bipolar disorder, lithium, divalproex

Clinical Medicine: Therapeutics 2009;1 657–667

This article is available from <http://www.la-press.com>.

© Libertas Academica Ltd.

This is an open access article distributed under the terms of the Creative Commons Attribution License (<http://www.creativecommons.org/licenses/by/2.0>) which permits unrestricted use, distribution and reproduction provided the original work is properly cited.

The authors grant exclusive rights to all commercial reproduction and distribution to Libertas Academica. Commercial reproduction and distribution rights are reserved by Libertas Academica. No unauthorised commercial use permitted without express consent of Libertas Academica. Contact tom.hill@la-press.com for further information.



Introduction

Bipolar affective disorder is a serious mental illness which is ranked as the fifth most disabling disease in the world by an influential WHO report,¹ and often has a chronic fluctuating course. Bipolar disorder is common, with a lifetime prevalence of 1.3%–1.6%, and more worryingly 10%–20% of individuals with bipolar disorder will commit suicide.² It has also been estimated that the annual cost to society of bipolar disorder in the UK is about £2 billion.³

The treatment of bipolar disorder usually requires psychotropic medication to reduce symptom severity, stabilize mood, and prevent relapse. Consideration of the different phases of bipolar illness is helpful when treatment is being instituted namely, acute phase—both manic and depressive; and long-term or maintenance phase treatment. Despite the relative paucity of high quality scientific data to aid prescribing, numerous guidelines exist around the world which summarise the expert view on the available evidence, as illustrated in Table 1. Table 1 shows that various expert committees have come to some rather differing conclusions as to the pharmacotherapy of the different phases of bipolar disorder, and also cannot make any recommendations for some phases (presumably due to limited data).

Second generation or ‘atypical’ antipsychotics are increasingly licensed (and used) for bipolar disorder as illustrated in Table 1, and also are known to be frequently used ‘off license’ in bipolar disorder.^{4,5} Initially these antipsychotics were proven to be effective in the treatment of acute phases of bipolar disorder, and more recently antipsychotic treatment studies have extended into the maintenance phase.⁶

Quetiapine is a second generation antipsychotic medication initially approved by the U.S. Food and Drug Administration in 1997 for the treatment of patients with schizophrenia, but due to its favorable side-effect profile it has been beneficially used across a range of mental disorders⁷ including mood disorders.⁵ The quetiapine molecule was originally modelled on clozapine, and has multi-receptor affinity. Colloquially it would appear to have a dose related ‘tri-phasic’ receptor uptake pattern, with sedative histaminic properties apparent at low dose (e.g. <200 mg per day); some antidepressant serotonergic and α -adrenergic effects seen at moderate dosages (e.g. 200–400 mg per day, although antidepressant effects at lower

doses has been described), and the antipsychotic dopaminergic properties being most apparent at higher daily doses (e.g. >400 mg per day). Jensen et al⁸ have also identified that a metabolite of quetiapine, *N*-desalkylquetiapine, is a potent norepinephrine (noradrenaline) reuptake inhibitor and partial 5-HT_{1A} agonist which could explain the antidepressant activity similar to tricyclic antidepressants.

Quetiapine is the only antipsychotic currently approved for use in the United States for the treatment of bipolar mania and bipolar depression, and quetiapine XR (or XL in Europe), which is a prolonged release variant of quetiapine allowing once daily dosing, is FDA approved for mixed state bipolar disorder and bipolar depression.

Here we examine the burgeoning evidence surrounding the use of quetiapine in bipolar disorder, both in the acute and maintenance phases of the illness. For example, at the beginning of 2009 an electronic search of medical databases using the keywords “quetiapine”; “seroquel”; “bipolar disorder”; and “manic depression” revealed 237 relevant matches. We critically review the available scientific data, consider the important gaps in the literature, and speculate about any future developments concerning quetiapine use in mood disorder.

Treatment of the Acute Phase of Bipolar Disorder

Treatment of acute mania

Current NICE Guidelines for the treatment of acute mania and hypomania recommend starting an antipsychotic, valproate or lithium (see Table 1). Only lithium, olanzapine, quetiapine, risperidone and valproate semi sodium are licensed for the acute treatment of mania in the UK. A meta-analytic review⁹ of randomized controlled trials looking at the use of second generation antipsychotics in the treatment of acute mania reviewed 24 studies (with 6187 patients included) and found that whilst the second generation antipsychotics displayed efficacy comparable with that of mood stabilisers, the most efficacious treatment was a combination of a mood stabiliser and a second generation antipsychotic.

A number of studies have looked at quetiapine monotherapy and quetiapine in combination with lithium or valproate semi sodium, otherwise known as divalproex, in the treatment of bipolar mania.



McIntyre et al¹⁰ found that quetiapine and haloperidol were equally efficacious as monotherapy for bipolar (type I) mania in a 12 week randomized trial, with the most effective dose range for quetiapine being 400–800 mg per day for resolution of manic symptoms according to the Young Mania Rating Scale (YMRS). A further study¹¹ evaluated the efficacy and tolerability of quetiapine monotherapy versus placebo for the treatment of mania over a 12 week period. This randomized, double blind, placebo—controlled study again used a reduction in YMRS as the primary outcome measure and concluded that quetiapine demonstrated superior efficacy to placebo in patients with bipolar mania and was well tolerated. Both these studies are summarised in Table 2.

The efficacy and tolerability of quetiapine in Chinese patients hospitalized with acute bipolar mania was compared to lithium over a 4 week period in a randomized double blind study.¹² 135 people completed the study, with YMRS as a primary endpoint. This study found that both response rate at 28 days and the overall remission rate were significantly greater with quetiapine than lithium which is arguably unexpected, although possibly these results cannot be generalised to other ethnicities.

Quetiapine combined with lithium or divalproex for the treatment of bipolar mania has been evaluated in three double-blind, placebo-controlled studies.^{13–15} Yatham et al¹³ perhaps unusually combined the results of an earlier randomized study¹⁴ with an identically designed later study “to increase power”. A total of 402 patients were randomized, with the primary outcome being improvement in the YMRS. At day 21 in the quetiapine plus lithium or divalproex was statistically superior to the placebo plus lithium/divalproex group. Improvements in the Clinical Global Impression-Bipolar severity of illness scores by day 21 were also significantly greater in quetiapine plus lithium/divalproex treated patients. However, a second trial by Yatham et al¹⁵ of quetiapine combined with lithium or divalproex showed an improvement in YMRS of only 2 points when compared with lithium/divalproex and placebo, and this was not statistically significant. These two trials by Yatham et al are summarized in Table 3.

A post hoc analysis¹⁶ of four similar, randomized, double-blind, placebo controlled trials of quetiapine in bipolar mania showed that quetiapine as

monotherapy, or in combination with lithium or semi-sodium valproate, was effective for acute mania and that quetiapine is efficacious even when medically serious symptoms are present. In all the studies mentioned above the daily dose range of quetiapine was between 300 and 800 mg.

Thus in summary, for acute bipolar mania, both quetiapine monotherapy and quetiapine in combination with a ‘mood stabiliser’ such as lithium or divalproex appear effective and well tolerated treatments. No study comparing quetiapine alone versus quetiapine plus a mood stabiliser has been identified and this would be useful in determining which is superior. Clinical experience and naturalistic work⁵ would suggest that combination therapy adds value, as recommended by meta-analysis,⁹ in terms of balancing symptom resolution against side effect profile.

Treatment of acute bipolar depression

The treatment of bipolar depression with quetiapine monotherapy was studied in two AstraZeneca funded trials known by the acronym BOLDER,^{17,18} conducted in the US. Both of these 8-week, placebo-controlled, double-blind studies compared two doses of quetiapine –300 mg per day and 600 mg per day, and included patients with bipolar I and bipolar II depressive episodes and eligible patients with histories of rapid cycling mood disorder. Both studies used change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score as the primary endpoint.

BOLDER I¹⁷ enrolled 542 patients meeting criteria for a current episode of bipolar I (n = 360) or bipolar II (n = 182) depression. 326 patients completed the 8 week study. Both doses of quetiapine resulted in significant improvements in MADRS total scores at all time points measured, with statistical significance over placebo detected after only 1 week of treatment (the first assessment point of the study) and maintained at every time point thereafter. The proportion of patients classified as responders to treatment, defined as a $\geq 50\%$ improvement in MADRS total score at study endpoint, was significantly higher in both groups receiving active quetiapine (58% in both groups) than in the group randomized to placebo (36%). Remission rates (defined as a final MADRS total score ≤ 12) followed a similar pattern (53% for both 300 mg and 600 mg quetiapine, 28% for placebo). Dry mouth,

Table 1. Guideline recommendations for pharmacotherapy in the various phases of bipolar disorder.

<i>Phase of bipolar</i>	BAP (British Association of Psychopharmacology)	SIGN (Scottish Intercollegiate Guidelines Network)	NICE (National Institute of Clinical Excellence)	WFSBP (World Federation of Societies of Biological Psychiatry)
<i>Mania</i>	1st = Oral AP or Valp mono (severe mania) ^{a,b} 1st = IM AP and Bnz (severe mania requiring parenteral Rx) ^{a,b} 1st = Li, Valp, Cbz or AP (less severe mania) ^b 2nd = Combo of Li or Valp with an AP ^c 2nd = Cloz in more refractory illness ^c	1st = Oral AP or Valp (mono) 1st = Li (mono) 1st = Li and AP combo	1st = AAP (Quet, Risp, Olz) (severe mania) ^h 1st = Li or Valp ^g (if prior good response) ^h 1st = Optimize treatment ⁱ 2nd = Add Li or Valp ^g to AAP (severe mania). 2nd = Add AAP (Quet, Rip Olz) ^j 3rd = Cbz ^h	1st = Li/Valp/AAP/Cbz ^{l,o} 1st = Li/Valp/Cbz ^{m,o} 2nd = Combination with a second MS or AAP ^{l,o,p} 2nd = Change of MS ^{l,o,q} 2nd = Combination of 2 MS, preferably anticonvulsant + Li ^{m,o} 3rd = Combination with a second MS or AAP ^{l,o}
<i>Mixed</i>	1st = Oral AP or Valp mono (severe mania) ^{a,b} 1st = IM AP and Bnz (severe mania requiring parenteral Rx) ^{a,b} 1st = Li, Valp, Cbz or AP (less severe mania) ^b 2nd = Combo of Li or Valp with an AP ^c 2nd = Cloz in more refractory illness ^c	Nothing specified	1st = Mood stabilizers (Dival, Olz, Cbz) 2nd = Add 2nd mood stabilizer	Brief summary provided in text. See full guidelines for details
<i>Depressed</i>	1st = Quet or Lamot (mild to moderate depression) ^b 1st = Add SSRI or other AD (not a TCA) to antimanic agent (Li, Valp or an AP) (moderate depression) ^{b,e} 1st = Add an AP (moderate depression) ^{b,bb} 1st = Li, Cbz, Valp, AP ^d 2nd = As selections 1–3 above ^d 2nd = Add an antimanic agent if BpDI ^b 3rd = Follow guidelines for UP depression	1st = AD in combo with an AP, Li or Valp 1st = Lamot	1st = AD (SSRI) + antimanic agent 1st Quet + non AP antimanic agent 2nd = Switch AD to mirt or Venlaf or add Quet or Ol (if not on AAP) 3rd =	1st = SSRI or bupropion + Li/ Lamot/Valp/Cbz ^{l,n} 1st = Selective MAO-I or new AD + Li/Lamot/Valp/Cbz ^{k,n} 2nd = SSRI or bupropion + Dual combination of MS ^{l,n} 2nd = Selective MAO-I or new AD + Dual combination of MS ^{k,n} 3rd = Change of AD, consider TCA or irreversible MAOI + Dual combination of MS, consider addition of thyroxine ⁿ
<i>Maintenance/ Relapse prevention/ Remission/ Euthymia</i>	1st = Li, mono ^{b,e} 2nd = Arp, Quet, Valp, Olz mono or combo of anti-manic agents (Li, Valp, AP) ^e 1st = Li mono ^f 2nd = Quet, Lamot mono ^f 3rd = Cbz ^e 3rd = Li ^f 4th or RC = Combination Rx ^{e,f}	1st = Li mono 1st Cbz mono (if Li not acceptable or for BpDI) 1st = Lamot mono (if stabilized on this)	1st = AAP, Li or Valp ^g 2nd = Li + Valp combo, Li + Olz combo, Valp + Olz 3rd = Consider Lamot (esp. BpDI) or Cbz	Li; AAP ^w ; Lamot ^x ; Valp, Cbz; 1st generation APs; Cloz; Risp ^y ; AD + MS ^{z,r} Li + Valp or Cbz; Li, Olz ^w ; Lamot ^x ; Cbz or Cloz; Nimodipine ^s Li; Cbz; Lamot, Valp; AD ^z ; AAP ^t Lamot; Valp; Cbz, Li; Nimodipine, AAP ^u Li, APP ^{aa} ; Cbz; Valp; AAP; 1st generation AP ^v



<i>Rapid cycling</i>	See maintenance Rx section above	1st = Li + Valp 2nd = Li mono 3rd = Consider Li or Valp + Lamot	Brief summary provided in text. See full guidelines for details
Notes: Mono: Monotherapy; AAP, Atypical antipsychotic; AD, Antidepressant; AP, Antipsychotic; Arp, Aripiprazole; Bnz, Benzodiazepine; Cbz, Carbamazepine; Cloz, Clozapine; Dival, Divalproex; IM, Intramuscular; Lamot, Lamotrigine; Li, Lithium; MAOI, Monamine Oxidase Inhibitor; Mirt, Mirtazapine; Olz, Olanzapine; Quet, Quetiapine; RC, Rapid cycling; Risp, Risperidone; Rx, Treatment; SSRI, Selective serotonin re-uptake inhibitor; TCA, Tricyclic antidepressant; UP, Unipolar; Valp, Valproate; Venlaf, Venlafaxine. ^aAtypical antipsychotics should be considered because of their generally more favorable short-term adverse event profile and the increasing evidence of their efficacy as anti-manic agents. ^bFor patients not already on long-term treatment for bipolar disorder. ^cFor patients who suffer a manic/mixed/depressive episode while on long-term treatment. ^dFor patients who suffer a depressive episode while on long-term treatment. ^eWhen mania is the burden of the illness. ^fWhen depression is the burden of the illness. ^gNot in women of child bearing potential. ^hThose not on anti-manic treatment. ⁱThose on anti-manic treatment. ^jModerate/severe depression. ^kSevere and/or psychotic depression. ^lMild to moderate mania. ^mSevere mania. ⁿAdjunctive treatment; + benzodiazepine, atypical antipsychotic or sleep deprivation. ^oAdjunctive treatment; + benzodiazepine or antipsychotic (preferably atypical). ^pPrevious maintenance treatment successful, but no acute response. ^qInitial treatment and prior maintenance unsuccessful. ^rBipolar I disorder without rapid cycling. ^sBipolar I with rapid cycling. ^tBipolar II without rapid cycling. ^uBipolar II with rapid cycling. ^vSchizoaffective disorder (bipolar type). ^wMania-dominant type. ^xDepression-dominant type. ^ySevere manias. ^zProminent depressions. ^{aa}Schizo-dominant type. ^{bb}If not already on an antipsychotic.			

**Table 2.** Quetiapine monotherapy versus placebo (pbo) and active comparator in mania.

Authors	McIntyre et al ¹⁰	Bowden et al ¹¹
Design	Pbo controlled RCT comparing quetiapine and haloperidol	Pbo controlled RCT comparing quetiapine and lithium
Setting	South America; Asia; Europe	Europe; Asia
Duration	12 weeks	12 weeks
Number individuals enrolled	302	302
% completed study (quetiapine: halo/Li: pbo)	55:55:42	67:68:36
YMRS:% response by study end (quetiapine: halo/Li: pbo)	61:70:39	72:76:41
CGI: % 'much' or 'very much' improved by study end (quetiapine: halo/Li: pbo)	51:60:30	72:72:37
Total (%) discontinuation due to adverse events (quetiapine: halo/Li: pbo)	5:10:6	6.5:6:4

sedation/somnolence, and dizziness were the common adverse events compared to placebo.

Cookson et al¹⁹ undertook a post-hoc analysis of BOLDER I, and showed that the 'number needed to treat'—a clinically relevant measure of how often one can expect a response—for quetiapine was five. This is impressively low, and reflects the underlying remission rates mentioned above. Furthermore, a secondary analysis of anxiety symptoms in BOLDER I²⁰ demonstrated that after 8 weeks both 300 mg and 600 mg of quetiapine significantly improved overall anxiety in those with bipolar I disorder.

Bipolar disorder is also associated with substantial impairment in health related quality of life, including

social and emotional functioning, occupational impairment and high utilization of healthcare services.²¹ BOLDER I and II also generated a post-hoc study²² of the effect on quality of life and sleep with quetiapine monotherapy in bipolar depression. Both the 300 mg and the 600 mg doses of quetiapine significantly improved quality of life and sleep by day 57, with the effect being more pronounced at the higher dose. These were subjective measures though, and it is possible that the quality of life improvement may simply reflect symptomatic improvement. Quetiapine therapy also led to significant improvement in quality of sleep compared with placebo which is not a huge surprise.

Table 3. Quetiapine or placebo (pbo) with lithium or divalproex in mania.

Authors	Yatham et al ¹³	Yatham et al ¹⁵
Design	Two pbo controlled RCTs combined	Pbo controlled RCT
Setting	Unspecified but incl. US	Europe; Canada; India
Duration of study	3 weeks	6 weeks
Number individuals enrolled	402	211
% completed study (quetiapine: pbo)	64:54	67:59
YMRS: response (%) by study end (quetiapine: pbo)	56:42	57:50
CGI:% 'much' or 'very much' improved by study end (quetiapine: pbo)	58.5:43	76:59
Total (%) discontinuation due to adverse events (quetiapine: pbo)	6:4	6:2



The results of the later BOLDER II study¹⁸ replicated the first study in terms of the primary outcome variable, with quetiapine-treated patients displaying significantly greater mean improvement in MADRS total scores than placebo-treated patients. 509 individuals were randomized in BOLDER II, and 301 completed the 8 week study, although here proportionately more dropped out from the quetiapine groups than placebo interestingly. Response rates for both doses of quetiapine monotherapy were also similar to those observed in the original study (60%, 58%, and 45% for the 300 mg, 600 mg, and placebo groups, respectively), as were remission rates (52% for both groups receiving quetiapine as compared to 37% for those receiving placebo). Again, dry mouth, sedation/somnolence, and dizziness were the common (short term) adverse events associated with quetiapine.

In both BOLDER studies the incidence of treatment emergence mania or hypomania was lower in the quetiapine treatment group than the placebo group, but the positive placebo response was higher in BOLDER II. The BOLDER studies concluded that quetiapine monotherapy is an effective and well tolerated treatment, over 8 weeks, for acute depressive episodes in bipolar disorder. Interestingly, the 300 mg daily dose appears to be more effective (and better tolerated) in bipolar depression than the 600 mg daily dose. The BOLDER studies are summarized in Table 4.

Suppes et al²³ conducted a placebo controlled RCT of quetiapine XL 300 mg per day as monotherapy for

bipolar (I or II) depression. This was an 8 week study with 133 and 137 (placebo) individuals enrolled, but is only available in abstract form thus far. The primary outcome was MADRS improvement, and a significant improvement with quetiapine XL versus placebo was found (−17.4 vs. −11.9) after 8 weeks treatment, although about 8% of those on quetiapine developed $\geq 7\%$ weight gain or high triglyceride levels.

To date, these encouraging results have not been confirmed in further work from AstraZeneca or elsewhere, although Oxford University (in the UK) have recently commenced a randomized pragmatic comparison of quetiapine monotherapy with lamotrigine and quetiapine combination—the two current front-runners for added efficacy in bipolar depression—called the CEQUEL trial.

Maintenance Pharmacotherapy in Bipolar Disorder

Suppes et al²⁴ compared quetiapine with placebo as an augmentation agent with either lithium or divalproex in a randomized double blind trial, as maintenance treatment for bipolar I disorder for a duration of up to 104 weeks. The primary outcome, after a 12 week run in phase, was recurrence of a ‘mood event’ (mania, depression, or a mixed episode) involving new medication. Hospitalization, study discontinuation, and significant change in the YMRS and MADRS were other outcomes studied. A total of only 176 patients completed the study from the 1953 individuals enrolled illustrating the complexity

Table 4. Quetiapine monotherapy versus placebo (pbo) in bipolar depression (BOLDER).

Authors	Calabrese et al ¹⁷	Thase et al ¹⁸
Design	Pbo controlled RCT	Pbo controlled RCT
Setting	USA	USA
Duration	8 weeks	8 weeks
Number individuals enrolled	542	509
% completed study (quetiapine: pbo)	61:59	56:65.5
MADRS (%) response (quet 600 mg: quet 300 mg: pbo)	58:58:36	58:60:45
CGI: % ‘much’ or ‘very much’ improved (quet 600 mg: quet 300 mg: pbo)	56:64:34	60:61:38.5
Total (%) discontinuation due to adverse events (quet 600 mg: quet 300 mg: pbo)	26:16:9	11:8:1



(and expense) of long term maintenance studies. Fewer individuals on quetiapine augmentation (20%) experienced a mood event compared to placebo (52%). Weight gain, sedation, and raised blood glucose were all more frequent in the quetiapine group. Study limitations included the (usual) exclusion of women who may become pregnant, and those with co-morbid medical illness or substance misuse, as well as selecting an 'enriched' sample of responders from the run-in phase.

Vieta et al²⁵ also separately studied quetiapine versus placebo as augmentation therapy with either lithium or divalproex in the prevention of recurrent 'mood events' in bipolar I disorder, again over up to 104 weeks. Here, 347 individuals (from a total enrolment of $n = 1461$) completed the study, with substantially more of the placebo group dropping out compared to quetiapine. Quetiapine again reduced the risk of a recurrent mood event compared to placebo (18.5% vs. 49%), corresponding to a relative risk reduction of relapse of 72%. Important adverse events noted, compared to placebo, after randomization in the quetiapine arm were weight gain, and a higher rate of emergent high fasting glucose. The same limitations as noted for the Suppes et al trial applied to this trial.

Taken together, these two published maintenance studies^{24,25}—summarised in Table 5—of augmenting lithium or divalproex with quetiapine offer convincing evidence of a significant reduction in relapse rate in bipolar I disorder, compared to lithium or divalproex monotherapy.

A further maintenance study in bipolar I disorder has been presented at conference, and compares quetiapine and lithium with placebo.²⁶ This study, which lasted a maximum of 104 weeks, indicates that quetiapine and lithium were equally effective maintenance treatments and both superior to placebo in reducing risk to a recurrent mood event, although the full study details are not yet in the public domain.

AstraZeneca also has two other studies^{27,28} of the maintenance treatment of bipolar depression, known by the acronym Embolden, which examine quetiapine and placebo with either lithium (Embolden I) or paroxetine (Embolden II). Unfortunately both these studies are only available in abstract form. Each study has two phases with over 500 patients, namely an acute phase replicating the BOLDER studies design and then a continuation phase where quetiapine responders were re-randomized to either quetiapine (300 mg) or placebo and studied for an additional 26–52 weeks. The abstracts indicate that quetiapine was more effective in reducing depressive symptoms compared with placebo or the other agents after an 8 week trial, although at this time little data on the maintenance phase treatment is in the public domain.

Other related work includes a naturalistic study from Italy,²⁹ where 232 individuals with either bipolar I or II were followed up for four years. Using survival analysis, they found that quetiapine (in low dose) plus lithium or valproate was superior compared to either monotherapy in maintaining euthymia (mood stability), although they acknowledged the limitations of a lack of randomization or control groups.

Table 5. Quetiapine or placebo (pbo) plus lithium/divalproex as bipolar maintenance therapy.

Authors	Vieta et al ²⁵	Suppes et al ²⁴
Design	RCT of quetiapine or pbo with lithium or divalproex	RCT of quetiapine or pbo with lithium or divalproex
Setting	Worldwide	USA and Canada
Duration	Upto 104 weeks	Upto 104 weeks
Number individuals randomized	706	628
% completed study (quetiapine: pbo)	63:37	35:21
% recurrent mood event (quetiapine: pbo)	18.5:49	20:52
Total (%) discontinuation due to adverse event (quetiapine: pbo)	2.4:3	11.3:2.6
% with weight gain >7% (quetiapine: pbo)	7.4:2	11.5:3.7



Finally, concerning the risk of diabetes in bipolar disorder, a long term retrospective review³⁰ from a large US medical claims database observed that the development or exacerbation of diabetes was associated with antipsychotic use in bipolar disorder. In particular, the hazard ratios (HR) were greatest for clozapine (HR = 7.0), with risperidone (HR = 3.4) and olanzapine (HR = 3.2) being intermediary, and quetiapine having an HR = 1.8. As always when prescribing, a risk/benefit balance needs to be achieved when a decision to prescribe is made, after discussion between the doctor and patient.

Quetiapine use in Bipolar Disorder with Comorbid Substance Misuse

Both alcohol and drug misuse are commonly seen in those with bipolar disorder, often representing self-medication and thrill seeking. Clinician reported rates of comorbid substance misuse, in 'real world' populations, can be up to 40% of all cases⁴ and constitutes a significant management problem which can exacerbate prognosis.

Nejtek et al³¹ studied 124 outpatients with cocaine or metamphetamine use or craving and bipolar (I or II) disorder who were entered into a randomized controlled trial comparing risperidone and quetiapine prescription. 80 outpatients were eligible for analysis, and both risperidone and quetiapine improved mood symptoms and reduced drug cravings equally. The absence of a control group, and the necessary use of inclusion and exclusion criteria in this study limit the generalizability of these findings. Brown et al^{32,33} also conducted two small open label pilot studies of quetiapine use in bipolar disorder with drug dependence, and found that drug use and craving reduced subsequent to quetiapine use.

The same group from Texas,³⁴ in a separate study, randomly assigned 115 outpatients with bipolar (I or II) disorder and alcohol abuse or dependence to quetiapine or placebo as 'add-on therapy'. Here, impressively, 102 outpatients lasted the 3 year study but quetiapine was no better than placebo in terms of reducing alcohol use or the YMRS score, although depressive symptoms (as measured by the Hamilton Rating Scale for Depression) did significantly improve with quetiapine use. A small 12 week open label study³⁵ examining quetiapine use in bipolar disorder with co-existent alcohol dependence did

however find a significant reduction in drinking at endpoint, although Longoria et al³⁶ found the number of alcoholic drinks did not diminish in 14 individuals with alcohol craving and bipolar disorder who were prescribed quetiapine. Again, this was a small short uncontrolled study.

Conclusions

Bipolar disorder is usually a chronic disabling condition requiring long term medication. Here we critically appraise the evidence surrounding the use of quetiapine in bipolar disorder—both in the acute and maintenance phases.

In the acute phase of bipolar disorder, there can be a serious risk of self harm, aggression, and even suicide, and medication is usually essential. When considering the use of quetiapine in acute bipolar disorder, there is convincing evidence supporting quetiapine therapy in acute bipolar I mania, at mid-to-high (i.e. 300–800 mg per day) dose, in combination with either lithium or divalproex.

With regard to the use of quetiapine in acute bipolar depression, the two BOLDER studies also support the use of quetiapine in acute bipolar depression, either as monotherapy or in combination with a mood stabiliser with the most effective daily dose of quetiapine being nearer to 300 mg than 600 mg. Ideally, however, the BOLDER studies should be independently replicated by other research groups to confirm these promising findings. In the future, we suspect that bipolar (I or II) depression may become (along with maintenance therapy) the primary indication for quetiapine use in bipolar disorder, and that quetiapine and lamotrigine³⁷ will become first line treatments for bipolar depression.

Turning to the long term maintenance medication for bipolar I and II disorder, the twin studies of Suppes et al, and Vieta et al provide persuasive evidence that quetiapine augmentation of either lithium or divalproex is an efficacious and safe strategy. Again, independent replication of these results would be desirable, and concerns over weight gain and emergent diabetes need to be further addressed although early evidence^{30,38} suggests that quetiapine is not the worst offender amongst second generation antipsychotics. These adverse event risks need to be balanced against the risks of un-treated or under-treated bipolar disorder mentioned above.



The prolonged release version of quetiapine (known as XR in the US and XL in Europe) is now available, and although it has the same half-life as the original quetiapine, it has a gel polymer ‘wrapping’ delaying gastro-intestinal release. Quetiapine XR is FDA approved for bipolar depression and mixed state bipolar disorder. It is worth noting that quetiapine XR/XL should be taken at least one hour before or after a meal, and dosing is straightforward—namely 300 mg on day 1 and 600 mg on day 2 for bipolar mania (and schizophrenia).

The data on quetiapine use in bipolar disorder with comorbid substance use are equivocal, so no firm recommendation can be made here. Nevertheless, this is a clinically important area that deserves further study, perhaps using innovative combinations of anti-craving drugs (e.g. naltrexone) and conventional bipolar therapies. Finally, we also expect to see future trials of quetiapine use in other mood disorders such as refractory depression and borderline or emotionally unstable personality.

Acknowledgment

The authors wish to thank Dr. JM Thompson, of AstraZeneca UK for help with Table 1. The views represented here are those of the authors.

Declaration of Interest

MT and PS have received hospitality and fees from pharmaceutical firms, including AstraZeneca, the manufacturers of quetiapine.

References

- Murray CJL, Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Cambridge, MA: Harvard University Press, 1996.
- Müller-Oerlinghausen B, Berghöfer A, Bauer M. Bipolar disorder. *Lancet*. 2002;359:241–7.
- NICE Bipolar Disorder. The management of Bipolar disorder in adults, children and adolescents in primary and secondary care clinical guideline. 2006.
- Taylor M, Shajahan P, Lawrie S. Comparing the use and outcomes of antipsychotics in clinical practice. *J Clin Psychiatry*. 2008;69(2):240–5.
- Shajahan P, Taylor M. Use and outcomes of quetiapine in depressive and bipolar mood disorders. *J Psychopharm*. Accepted for publication 2009.
- Young AH. Treatment of bipolar disorder with antipsychotic medication: issues shared with schizophrenia. *J Clin Psychiatry*. 2007;68(suppl 6):24–5.
- Adityanjee, Schulz SC. Clinical use of quetiapine in disease states other than schizophrenia. *Journal of Clinical Psychiatry*. 2002;63(suppl 13):32–8.
- Jensen NH, Rodriguiz RM, Caron MG, et al. *N*-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT_{1A} agonist, as a putative mediator of quetiapine’s antidepressant activity. *Neuropsychopharmacology*. 2008;33:2303–12.
- Scherk H, PajonkFG, Leucht S. Second generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Archives of General Psychiatry*. 2007;64(4):442–55.
- McIntyre RS, Brecher M, Paulsson B, et al. Quetiapine or haloperidol as monotherapy for bipolar mania—a 12 week double blind randomised parallel group, placebo controlled trial. *Euro Neuropsychopharm*. 2005;15(5):573–85.
- Bowden CL, Grunze H, Mullen J, et al. A randomized, double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. *Journal of Clinical Psychiatry*. 2005;66(1):111–21.
- Li H, Ma C, Wang G, Zhu X, Peng M, Gu N. Response and remission rates in Chinese patients with bipolar mania treated for four weeks with either quetiapine or lithium : a randomized and double blind study. *Current Medical Research and Opinion*. 2008;24(1):1–10.
- Yatham LN, Paulsson B, Mullen J, Vagero M. Quetiapine versus placebo in combination with Lithium or Divalproex for the treatment of bipolar mania. *Journal of Clinical Psychopharmacology*. 2004;24(6):599–606.
- Sachs GA, Chengappa K, Suppes T, et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania : a randomised double blind, placebo-controlled study. *Bipolar Disorders*. 2004;6(3):213–23.
- Yatham LN, Vieta E, Young AH, Moller HJ, Paulsson B, Vagero M. A double blind, randomised, placebo controlled trial of quetiapine as an add-on therapy to lithium or divalproex for the treatment of bipolar mania. *International Clinical Psychopharmacology*. 2007;22(4):212–20.
- McIntyre RS, Konarski JZ, Jones M, Paulsson B. Quetiapine in the treatment of acute bipolar mania: efficacy across a broad range of symptoms. *Journal of Affective Disorders*. 2007;100 Suppl 1:s5–14.
- Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162:1351–60.
- Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol*. 2006;26:600–9.
- Cookson J, Keck PE, Ketter TA, Macfadden W. Number needed to treat and time to response/remission for quetiapine monotherapy efficacy in bipolar depression: evidence from a large randomised, placebo-controlled study. *Int Clin Psychopharmacology*. 2007;22(2):93–100.
- Hirschfield RMA, Weisler RH, Raines SR, et al. Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: a secondary analysis from a randomised double blind placebo controlled study. *J Clin Psychiatry*. 2006;67:335–62.
- Dean BB, Gerner D, Gerner RH. A systematic review evaluating health-related Quality of Life, work impairment, and healthcare costs and utilization in bipolar disorder. *Current Medical Research Opinion*. 2004;20:139–54.
- Endicott J, Paulsson B, Gustafsson U, et al. Quetiapine monotherapy in the treatment of depressive episodes of bipolar I and II disorder: improvements in quality of life and quality of sleep. *J Affective Disorders*. 2008;111:306–19.
- Suppes T, Datto C, Minkwitz M, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. Presented at the 8th annual Int Review of Bipolar Disorders conference; April 14–16, 2008; Copenhagen, Denmark.
- 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(4):476–88.
- Vieta E, Suppes T, Eggens 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 Affective Disorders*. 2008;109:251–63.
- Weisler RH, Nolen WA, Neijber A, et al. Quetiapine or lithium versus placebo for maintenance treatment of bipolar I disorder after stabilisation on quetiapine. 60th Inst Psychiatric Services Congress; Oct 2–5, 2008, Chicago, USA.



27. Young A, Carlsson A, Olansson B, et al. A double blind, placebo controlled study with acute and continuation phase of quetiapine and lithium in adults with bipolar depression (EMBOLDEN I) (abstract NR3—004) American Psychiatric Association 2008 Annual Meeting.
28. Olansson B, Young A, Carlsson A, et al. A double blind, placebo controlled study of quetiapine and Paroxetine in adults with bipolar depression (EMBOLDEN II) (abstract NR3—013) American Psychiatric Association 2008 Annual Meeting.
29. Altamura AC, Mundo E, Dell’Osso B, et al. Quetiapine and classical mood stabilisers in the long term treatment of bipolar disorder: a 4 year follow-up naturalistic study. *J Affective Disorders*. 2008;110(1–2):135–41.
30. Guo JJ, Keck PE, Corey-Lisle PK, et al. Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorder: a retrospective population based, case-control study. *J Clin Psychiatry*. 2006;67(7):1005–61.
31. Nejtek VA, Avila M, Chen LA, et al. Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? *J Clin Psychiatry*. 2008;69(8):1257–66.
32. Brown ES, Nejtek VA, Perantie DC, et al. Quetiapine in bipolar disorder and cocaine dependence. *Bipolar Disorders*. 2002;4(6):406–11.
33. Brown ES, Nejtek VA, Perantie DC. Cocaine and amphetamine use in patients with psychiatric illness. *J Clin Psychopharmacol*. 2003;23(4):384–88.
34. Chiu SS. Quetiapine in bipolar disorder with alcohol dependence: a pilot study [abstract] Presented, 159th APA, May 20–25, Toronto, Canada
35. Longoria J, Brown ES, Perantie DC, et al. Quetiapine for alcohol use and craving in bipolar disorder. *J Affective Disorders*. 2004;78(suppl 1): S106, Abs P10.
36. Brown ES, Garza M, Carmody TJ. A randomised double-blind, placebo-controlled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. *J Clin Psychiatry*. 2008;69(5):701–5.
37. Geddes J, Calabrese JC, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Brit J Psychiatry*. 2009;194:4–9.
38. Patel JK, Buckley PF, Woolson S, et al. Metabolic profiles of second generation antipsychotics in early psychosis: findings from the CAFÉ study. *Schizophr Research*. 2009;111:9–16.

Publish with Libertas Academica and every scientist working in your field can read your article

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

<http://www.la-press.com>