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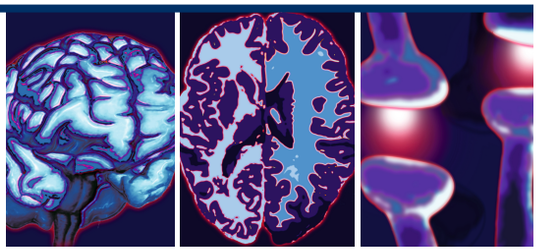

Extended-release quetiapine fumarate in the treatment of bipolar disorder

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Practice points

- Extended-release quetiapine fumarate is used in bipolar disorder in acute mania and in the maintenance phase (as monotherapy or as an adjunct to divalproex or lithium) and in bipolar depression (as monotherapy).
- Dose ranges from 300 mg daily in bipolar depression to 400–800 mg daily in mania or mixed episodes. The dose at which stabilization is reached is continued in the maintenance phase.
- Best administered once daily, 4–5 h before bedtime; meals are best avoided at the time of administering the drug.
- Use during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus; the assessment for abnormal glucose tolerance in pregnancy is advised. Women receiving the drug should not breastfeed and prescription in the elderly should be cautious. It is not indicated for those under 18 years of age.
- Monitoring of metabolic parameters is recommended.

SUMMARY The management of bipolar disorder presents challenges for the clinician who is often required to prescribe a variety of medication regimes for the different phases of the illness. With a range of pharmacological actions, quetiapine fumarate is a useful option in such circumstances. Initial studies have yielded encouraging results: quetiapine fumarate is effective as monotherapy or as an adjunct to mood stabilizers in mania and in the maintenance phase, and as monotherapy in bipolar depression. The extended-release preparation with once-daily dosing may potentially enhance adherence. Studies of this formulation reveal an efficacy profile matching the immediate-release preparation. However, precise dosing schedules, metabolic consequences and the risk of other side effects will need to be considered in establishing quetiapine fumarate in the management of any individual patient.

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Bipolar disorder is a chronic illness marked by cyclical changes in mood. Two main clinical types have been recognized: bipolar I disorder, characterized by one or more manic episodes, and bipolar II disorder, characterized by milder 'hypomanic' episodes. Depressive episodes are almost universal in both types of bipolar disorder; indeed, the depressed phase is usually the predominant mood state over the life course [1]. A lifetime prevalence of 2–3%, an equal distribution among the sexes and an estimated 10–20% mortality from suicide, underscores the importance of bipolar disorder as a major mental disorder [2,3].

The management of bipolar disorder is rendered complex due to the phasic nature of the illness with different medications often being needed for the various phases and stages and with clinicians often relying on combinations of antipsychotics, antidepressants and mood stabilizers. Treatment is aimed at reducing the severity of symptoms in the acute phase, maintaining a stable mood and preventing relapses.

Despite a wide range of drugs being licensed for treatment, specific regimes for the various phases and stages of bipolar disorder have not evolved satisfactorily. Numerous guidelines have been derived for the purpose, but propose different pharmacotherapeutic strategies for the various phases [4].

Quetiapine fumarate (hereinafter referred to as quetiapine), initially an antipsychotic used in the treatment of schizophrenia, has emerged as a treatment option in bipolar disorder following the demonstration of its efficacy in a broad spectrum of mental disorders [5]. Its value in the treatment of mania and bipolar depression, as well as its mood stabilizing properties, provides enhanced utility as a therapeutic agent in the various stages of the illness and has led to an increase in its use in bipolar disorder. More recently an extended-release (ER) formulation has been developed, with the practical benefit of once-daily dosing.

This report reviews the available evidence on the role of a quetiapine ER preparation in bipolar disorder, both in the context of its potential advantages, such as once-daily dosing and improved adherence, as well as its possible drawbacks, such as significant metabolic consequences and broader side-effect profiles.

Indications & usage

Quetiapine ER, is initially licensed for the treatment of bipolar disorder in several phases. It is used as monotherapy in the management of bipolar depression and may be used as monotherapy or as an adjunct treatment to lithium or divalproex in acute mania or in the maintenance treatment of bipolar I disorder. In the USA, mixed episodes in bipolar I disorder are also listed as an indication [101].

Dosage & administration

Quetiapine ER is available in strengths of 50, 150, 200, 300 and 400 mg. A once-daily dose of 300 mg reached over a period of 4 days is often used in the treatment of bipolar depression. A once-daily dose of 400–800 mg reached over a period of 3 days is used in the treatment of acute mania or mixed episodes, titrated according to need **(Table 1)**. It is generally recommended that the dose reached in the stabilization phase should be continued when the drug is used in the maintenance treatment of bipolar I disorder [101]. However, specific details regarding dosing are still unclear. There is no consensus on the duration of maintenance treatment, nor is there agreement on how the drug should be titrated following a depressive episode; these are left at the discretion of the clinician. These are a potential hindrance to effective prescribing and would benefit from more detailed study.

Clinical pharmacology

Mechanism of action

The affinity of quetiapine ER to multiple receptors including histamine, α_2-adrenergic autoreceptors, serotonin $5HT_{1A}$ and $5HT_{2A}$ receptors, and dopamine D_1 and D_2 receptors may explain its effectiveness as a therapeutic agent, both in bipolar disorder and schizophrenia. Its antagonism at muscarinic M_1 receptors can explain its anticholinergic effects [101].

Pharmacodynamics

It has been proposed that the efficacy of quetiapine ER in bipolar depression is due to a metabolite, *N*-desalkylquetiapine, also known as norquetiapine, having a relatively high affinity for the norepinephrine uptake transporter, thereby acting as a norepinephrine reuptake inhibitor. When a steady state of the drug is reached, the norquetiapine:quetiapine ratio is approximately 1:3 and the antidepressant effect of quetiapine is seen at doses of approximately 300 mg [6]. The mood-stabilizing properties of the drugs are thought to be due to D_2 and $5HT_{2A}$ receptor antagonism [7].

Comparisons between the ER preparation and the immediate-release (IR) preparation have been attempted. PET studies have revealed that once-daily dosing of the ER formulation leads to central D_2-receptor occupancy comparable to twice-daily dosing of the IR formulation [8]. However, the implications of these findings in terms of clinical efficacy or adverse effects is yet to be fully established.

■ Pharmacokinetics

Quetiapine ER is well absorbed and the peak concentration is proportional to the drug's dose. The drug is extensively metabolized in the liver with the involvement of cytochrome P450 enzymes with a mean terminal half-life of approximately 7 h for quetiapine and 12 h for norquetiapine [101].

PET studies indicate that once-daily dosing of the ER formulation gives peak and trough plasma levels comparable to twice-daily dosing of the IR formulation [8]. The clinical implications of this finding have not been confirmed.

It has also been demonstrated that modifying the formulation into an ER form does not change the overall absorption or elimination of quetiapine and does not lead to unexpected adverse effects, thereby supporting its use as a once-daily treatment in patients initiating therapy, or as an alternative for those established on the IR form. It must, however, be noted that these findings were from a 10-day, single-center study [9].

A clinically significant property of the quetiapine ER preparation is that peak plasma concentrations occur several hours after administration. Hence, quetiapine ER needs to be administered 4–5 h before bedtime for peak concentrations to be reached during sleep in contrast to the IR preparation, which is administered 30–60 min before bedtime [10]. It is also best that the drug is not taken with a large meal as high-lipid concentrations in the GI tract may accelerate the release of the ER preparation [101].

Table 1. Recommended dosing schedules for extended-release quetiapine fumarate in bipolar disorder.

Day	Bipolar depression (mg)	Acute mania (mg)
1	50	300
2	100	600
3	200	400–800
4 onwards	300	400–800

Clinical evidence

■ Overview of clinical trials

Quetiapine was initially assessed for its efficacy in the treatment of bipolar disorder in its IR form. Several studies evaluated the drug's impact in the treatment of acute mania, bipolar depression and in maintenance therapy. Following promising outcomes, its ER formulation has also been assessed for its efficacy in three major studies.

The major studies evaluating quetiapine in bipolar disorder are listed in Table 2. This overview discusses the findings of studies utilizing quetiapine IR prior to reviewing the studies that used the ER formulation. Finally, a study that compares the IR and ER formulations is discussed.

Studies assessing the efficacy of quetiapine IR in the treatment of mania in bipolar disorder

Table 2. Major studies evaluating preparations of quetiapine fumarate in bipolar disorder.

Author (year)	Drugs evaluated	Phase of bipolar disorder	Ref.
McIntyre *et al.* (2005)	Quetiapine IR, haloperidol	Mania	[11]
Bowden *et al.* (2005)	Quetiapine IR, lithium	Mania	[12]
Li *et al.* (2008)	Quetiapine IR, lithium	Mania	[13]
Yatham *et al.* (2004)	Quetiapine IR or placebo with lithium or divalproex	Mania	[14]
Sachs *et al.* (2004)	Quetiapine IR or placebo with lithium or divalproex	Mania	[15]
Yatham *et al.* (2007)	Quetiapine IR or placebo with lithium or divalproex	Mania	[16]
Calabrese *et al.* (2005)	Quetiapine IR, placebo	Depression	[17]
Thase *et al.* (2006)	Quetiapine IR, placebo	Depression	[18]
Vieta *et al.* (2008)	Quetiapine IR or placebo with lithium or divalproex	Maintenance	[19]
Suppes *et al.* (2009)	Quetiapine IR or placebo with lithium or divalproex	Maintenance	[20]
Weisler *et al.* (2011)	Quetiapine IR, lithium, placebo	Maintenance	[21]
Cutler *et al.* (2011)	Quetiapine ER, placebo	Mania	[22]
Suppes *et al.* (2010)	Quetiapine ER, placebo	Depression	[23]

ER: Extended release; IR: Immediate release.

have suggested it is a useful agent in this phase. McIntyre *et al.* conducted a 12-week double-blind, randomized placebo-controlled trial and found quetiapine IR to be as effective as haloperidol [11]. A study with a similar design by Bowden *et al.* suggested that quetiapine IR was as effective as lithium [12]. Li *et al.* reported that quetiapine IR was superior to lithium in a randomized, double-blind study [13].

Studies have also demonstrated the value of quetiapine IR in combination with lithium or divalproex in the treatment of mania. Three double-blind, placebo-controlled studies assessed the efficacy of quetiapine IR compared with placebo, in combination with lithium or divalproex [14–16]. Two studies concluded that quetiapine IR, in combination with lithium or divalproex had a superior efficacy to lithium or divalproex monotherapy in the treatment of bipolar mania. Outcome measures, as assessed by changes in the Young Mania Rating Scale in the third study, were favorable for quetiapine IR, but statistically not significant [16].

The efficacy of quetiapine IR in the management of bipolar depression has been assessed in two studies known as the 'BOLDER' I and II studies. Both were 8-week, placebo-controlled, double-blind studies comparing two doses of once-daily bedtime quetiapine IR, 300 and 600 mg per day, and included patients with bipolar I and II depressive episodes. They recorded similar and significant reductions in the Montgomery–Asberg Depression Rating Scale scores, suggesting that both doses of quetiapine IR were significantly more effective than placebo in bipolar depression. These studies were of a relatively short duration and the BOLDER II study had a 41% dropout rate [17,18].

Two randomized double-blind trials compared quetiapine IR with placebo as an augmentation agent with either lithium or divalproex as maintenance treatment for bipolar I disorder, where the primary outcome was a recurrence of a manic, depressed or mixed episode. Both studies reported that augmenting lithium or divalproex with quetiapine IR significantly reduced the relapse rate in bipolar I disorder compared with lithium or divalproex monotherapy [19,20].

Weisler *et al.* investigated relapse prevention in patients who had received quetiapine IR as monotherapy for a recent manic, depressive or mixed episode. They were randomly assigned to quetiapine IR monotherapy, lithium or placebo. Outcomes measured as a recurrence of a mood event were significantly better with both quetiapine IR monotherapy and lithium compared with placebo [21].

Recent studies have attempted to evaluate the effectiveness of quetiapine ER in bipolar disorder. The findings of these studies, which were of a relatively short duration, are summarized in **Table 3**.

Cutler *et al.* reviewed the efficacy of quetiapine ER as monotherapy in acute mania in a randomized, double-blind, placebo-controlled study and concluded that quetiapine ER monotherapy significantly improved symptoms in acute mania,

Table 3. Summary of studies evaluating extended-release quetiapine fumarate in bipolar disorder.

Characteristic	Cutler *et al.*[†]	Suppes *et al.*[‡]
Study	Monotherapy in acute mania	Monotherapy in bipolar depression
Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Setting (country)	USA	USA
Duration (weeks)	3	8
Number of participants	308	270
Quetiapine fumarate ER dose (mg)	400–800 (mean = 604)	300
Primary outcome measure	YMRS total score at week 3	MADRS total score at week 8
Conclusion	Quetiapine fumarate ER once-daily monotherapy effective and well tolerated in mania	300 mg quetiapine fumarate ER once-daily monotherapy effective and well tolerated in bipolar depression
Reported adverse effects	Sedation, dry mouth and somnolence	Sedation, dry mouth, somnolence and weight gain compared with placebo

ER: Extended release; MADRS: Montgomery–Asberg Depression Rating Scale; YMRS: Young Mania Ratings Scale.
[†]Data taken from [22].
[‡]Data taken from [23].

as measured by the Young Mania Rating Scale total score. The formulation was well tolerated with mild-to-moderate side effects, the most common reported being sedation, dry mouth and somnolence [22].

The effectiveness of quetiapine ER as monotherapy in bipolar depression was studied by Suppes *et al.* who reported that 300 mg once-daily monotherapy of quetiapine ER was significantly more effective than placebo for treating episodes of depression in bipolar I disorder. The most common adverse effects were dry mouth, somnolence and sedation. A greater weight gain was also noted in patients on quetiapine ER, relative to placebo [23].

In clinical practice, the use of quetiapine ER needs to be informed by establishing its efficacy and tolerability in comparison with quetiapine IR. There is a paucity of such comparisons and only one direct comparison study could be found. This multicenter European study compared the hospital stays in patients admitted for an acute bipolar manic episode and treated with either quetiapine IR or quetiapine ER. The outcomes suggest that the length of hospital stay was not associated with the type of quetiapine received [102].

The findings reviewed above converge in the view that quetiapine IR is useful in the treatment of bipolar disorder, as monotherapy in the treatment of mania and bipolar depression and as an adjunct with lithium or divalproex in the treatment of mania, as well as in maintenance therapy. More recent studies with quetiapine ER appear to demonstrate findings similar to those from studies using the IR formulation. However, only a single head-to-head comparison between the two formulations exist; conclusions need to be tempered.

■ Adverse reactions

In the study by Suppes and colleagues, the most commonly reported side effects from quetiapine ER used in bipolar depression were dry mouth, sedation and somnolence, while increased appetite, headache, constipation and nausea were also reported [23]. Cutler *et al.* reported the common side effects of sedation, dry mouth, somnolence and headache due to quetiapine ER used in mania [22].

Extrapyramidal side effects have been noted in 4.4% of patients with the use of quetiapine ER in the mania study compared with 0.7% in those on placebo [22].

Weight gain was monitored in studies that utilized the ER formulation. A bodyweight increase of over 7% was reported in 8.2% of subjects receiving 300 mg quetiapine ER compared with 0.8% in those receiving placebo in the 8-week bipolar depression study [23]. In the 3-week mania study, a bodyweight increase of over 7% was seen in 5.1% of subjects receiving 400–800 mg quetiapine ER, compared with no increase in the placebo arm [22].

Among metabolic side effects, the most noticeable in the two studies using quetiapine ER was an elevation in fasting blood glucose. In the mania study, at the end of 3 weeks, 4.1% of quetiapine ER treated subjects had a significantly high-fasting blood-glucose level compared with only 1.6% of those treated with placebo. In the bipolar depression study, at its conclusion after 8 weeks, 5.8% of quetiapine ER treated subjects showed a significant increase in fasting glucose levels compared with 2.4% of those treated with placebo [22,23].

The drug carries a warning by the manufacturer regarding increased mortality in patients with dementia-related psychosis treated with atypical antipsychotics. It also carries a warning about the potential for increased suicidality in children, adolescents and young adults treated with antidepressants [101]. While both recommendations are generic and not specific to quetiapine, the use of the agent in the younger and older populations require requisite caution and careful monitoring.

The manufacturers also caution against two other serious side effects, namely tardive dyskinesia and neuroleptic malignant syndrome [101]; however, the magnitude of the risk of developing these side effects has not been established.

Of particular concern are reports of QT prolongation with quetiapine in overdose, in patients with medical comorbidities and in those on other medications known to cause electrolyte imbalance or increase the QT interval [101].

In short-term clinical trials, other uncommon side effects that have been reported with quetiapine ER include seizures, hypothyroidism, hyperprolactinemia, serum transaminase elevation and cognitive and motor impairment [101].

The side-effect profile of quetiapine ER also includes dry mouth, sedation and somnolence as common side effects, while the incidence of extrapyramidal side effects appears to be low compared with other antipsychotics. However, there is significant potential for metabolic side

effects, especially weight gain and elevation of blood glucose.

■ Drug interactions

Quetiapine ER has relatively few drug interactions, but its effects on other centrally acting drugs must be noted as they are often prescribed together. The concomitant prescribing of quetiapine ER with divalproex leads to a reduction in valproic acid levels by 10% and up to a 17% increase in quetiapine levels. The simultaneous prescription of lithium with quetiapine ER has no clinically significant effects [101].

Quetiapine ER may also be safely prescribed with fluoxetine, imipramine, haloperidol and risperidone. A reduced dosage of quetiapine ER may be indicated when it is prescribed with drugs that inhibit cytochrome P450 3A, such as ketoconazole and erythromycin [101].

■ Use in specific populations

Data on the use of quetiapine ER in pregnancy and lactation are scarce and its use in these circumstances is recommended only if the expected benefits outweigh the potential risks. Quetiapine ER is not approved for use in patients under 18 years of age [101].

There have been no indications of a different degree of tolerability to quetiapine ER in the elderly, but a lower starting dose, slower titration and close monitoring during the initial phase of treatment is generally recommended. Dosage adjustment may also be necessary when prescribing quetiapine ER to those with hepatic impairment as the drug is extensively metabolized in the liver [101].

Clinical & practical issues

Quetiapine provides the clinician dealing with mental disorders with a drug that is effective and with many uses. Being primarily an antipsychotic, initially used exclusively in the treatment of schizophrenia, its value lies in several attributes, a relatively mild side-effect profile in terms of extrapyramidal side effects and a wider dose range being among them.

With its empirical use in a range of mental disorders yielding satisfactory results, the use of quetiapine in bipolar disorder has been a recent focus of study, more so because quetiapine appears to meet the peculiar demands of the illness, which is phasic by nature, needing different treatment strategies for its varying stages.

Initial study results, although not by any means comprehensive or conclusive, have been encouraging. In a series of randomized, controlled trials, quetiapine shows promise of being effective as monotherapy in mania, bipolar depression and in the maintenance phase. As an adjunct to lithium or divalproex, it has shown consistent efficacy in mania and in the maintenance phase of bipolar disorder.

While the majority of these studies utilized the IR formulation of quetiapine, the ER formulation of the drug is also being investigated. The prospect of once-a-day dosing with potential for enhanced adherence suggests that this preparation may be of particular value.

The need to ascertain whether the change of formulation of quetiapine from IR to ER leads to any specific therapeutic or side effect advantages or disadvantages to patients will be paramount. The ER formulation has been found to be effective in mania and bipolar depression in those studies in which its performance has been reviewed. An initial head-to-head comparison between the two formulations does not appear to favor one formulation over the other and more studies on this aspect are a necessity.

More evidence is also needed to firmly establish the efficacy of quetiapine ER in the management of the different stages of bipolar disorder to enable clinicians to opt for the drug with a greater degree of confidence. Its role, in particular as an adjunct to more established mood stabilizers, needs further clarification.

Other issues, such as the potential for metabolic side effects including hyperglycemia and weight gain, need to be borne in mind by prescribers, and psychoeducation and metabolic mentoring should be mandated [24]. The level of risk from potentially serious adverse effects needs further clarification. Precise information for prescribers in the form of dosing regimens and duration of treatment is also required.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

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