https://www.mediresonline.org/

ISSN: 2836-3558

Open Access

Psychiatry and Psychological Disorders

Research Article

Quetiapine in Bipolar Disorder: Clinical Pharmacology, Receptor Pharmacology, And The Mechanistic Basis of Its Antidepressant And Mood-Stabilizing Effects

Michel Bourin[1]*

[1]Neurobiology of Anxiety and Mood Disorders, Nantes University, 98 rue Joseph Blanchart, 44100 Nantes, France.

***Corresponding Author:** Michel Bourin, Neurobiology of Anxiety and Mood Disorders, Nantes University, 98 rue Joseph Blanchart, 44100 Nantes, France.

Received Date: 02 October 2026; **Accepted Date:** 26 October 2026; **Published Date:** 02 November 2026

Copyright: © 2026 Michel Bourin, this is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Quetiapine is an atypical antipsychotic with established efficacy across several phases of bipolar disorder, including acute bipolar depression, acute mania, and maintenance treatment. Its clinical profile is unusual among antipsychotic drugs because clinically relevant antidepressant activity occurs at doses that do not simply correspond to conventional high-level dopamine D^2 receptor blockade. The pharmacology of quetiapine is further complicated by the formation of the active metabolite N-desalkylquetiapine (norquetiapine), whose receptor and transporter profile differ substantially from that of the parent compound. Consequently, the therapeutic effects of quetiapine are better conceptualized as the result of a pharmacologically integrated parent-drug/metabolite system rather than because of D^2 antagonism alone. The present review examines the clinical pharmacology of quetiapine in bipolar disorder, with particular emphasis on the mechanistic basis of its antidepressant effects. Quetiapine antagonizes dopamine D^2 and serotonin 5-HT^2A receptors and interacts with histamine H^1, α^1-adrenergic and muscarinic receptors. Norquetiapine has relatively greater affinity for several of these targets and, importantly, inhibits the norepinephrine transporter (NET) and exhibits partial agonist activity at 5-HT^1A receptors. Human positron-emission tomography studies provide evidence that clinically relevant quetiapine exposure produces measurable NET occupancy, supporting a role for noradrenergic modulation in the antidepressant response. Preclinical data further suggests interactions with serotonergic, dopaminergic and noradrenergic neurotransmission, while proposed effects on intracellular signalling, neuroplasticity and circadian regulation remain less firmly established. Clinical trials consistently demonstrate that quetiapine is superior to placebo in acute bipolar depression, with antidepressant effects detectable during the first week of treatment. Both immediate-release and extended-release formulations have demonstrated efficacy, while higher doses have consistently produced greater antidepressant benefit than approximately 300 mg/day in acute bipolar depression. Quetiapine is also effective in relapse prevention, particularly for depressive recurrence, although interpretation of maintenance trials must account for enrichment and discontinuation designs. The principal limitation of quetiapine is its tolerability profile, particularly somnolence, sedation, orthostatic hypotension, weight gain and metabolic abnormalities. These adverse effects can be understood partly through its receptor pharmacology, especially H^1, α^1-adrenergic and muscarinic antagonism. Overall, quetiapine represents a pharmacologically complex treatment whose antidepressant activity cannot be adequately explained by its antipsychotic D^1 antagonism. The most coherent current model involves complementary serotonergic, noradrenergic and dopaminergic effects generated by the parent drug and norquetiapine, while acknowledging that the precise molecular mechanism responsible for clinical antidepressant and mood-stabilizing efficacy remains unresolved.

Keywords: Maladaptive Hyper-attachment Syndrome, N-of-1 Assay, Free Energy Principle, Brain Thermodynamics, AM404, Quetiapine.

Introduction

Bipolar disorder is characterized by recurrent episodes of depression and mania or hypomania, with depressive morbidity accounting for a substantial proportion of the symptomatic burden [1]. Pharmacological treatment is consequently required to address two apparently opposing therapeutic objectives: suppression of pathological activation and prevention of recurrence while simultaneously treating depressive symptoms without precipitating a manic or hypomanic switch. The pharmacological treatment of bipolar depression has historically been more problematic than the treatment of mania [2]. Conventional antidepressants have limitations in bipolar disorders, particularly because treatment-emergent affective switching and cycle acceleration remain important clinical concerns in selected patients[3]. Consequently, drugs capable of treating depressive symptoms while simultaneously providing antimanic or mood-stabilizing activity are particularly valuable. Quetiapine occupies a distinctive position within this therapeutic landscape. Contemporary CANMAT/ISBD recommendations place quetiapine among the principal first-line treatments for acute bipolar I depression, while quetiapine is also a first-line option for bipolar II depression and maintenance treatment [4]. The clinical efficacy of quetiapine is particularly interesting from a pharmacological perspective because its antidepressant properties cannot readily be attributed to conventional antipsychotic D^2 receptor antagonism. Instead, quetiapine possesses a broad receptor-binding profile, and its metabolism generates norquetiapine, a pharmacologically active compound with substantial activity at targets implicated in antidepressant pharmacology [5]. This distinction is critical: the mechanism of action of quetiapine in bipolar depression should not be regarded as synonymous with the mechanism by which D^2 antagonists suppress psychosis or mania. The objective of this review is therefore to integrate the clinical and molecular pharmacology of quetiapine and to develop a mechanistically coherent model of its therapeutic action in bipolar disorder.

Pharmacological Position of Quetiapine in Bipolar Disorder

Quetiapine is a dibenzothiazepine-derived second-generation antipsychotic. Unlike several other atypical antipsychotics, its clinical spectrum includes clinically meaningful efficacy against depressive symptoms in both bipolar I and bipolar II disorder[6]. The evidence base supporting this indication derives from multiple randomized, double-blind, placebo-controlled trials. In the BOLDER II study, quetiapine 300 and 600 mg/day produced significantly greater improvement in depressive symptoms than placebo, with separation from placebo evident from the first week of treatment [7]. Similarly, the EMBOLDEN II trial randomized 740 patients with bipolar I or bipolar II depression to quetiapine 300 mg/day, quetiapine 600 mg/day, paroxetine 20 mg/day, or placebo. Both quetiapine doses produced significantly greater reductions in Montgomery–Åsberg Depression Rating Scale scores than placebo, whereas paroxetine did not significantly separate from placebo on the primary endpoint [8]. These findings have been replicated across a broader evidence base. A systematic review and meta-analysis of 11 randomized controlled trials involving 3,488 participants found significantly greater improvement in depressive symptoms with quetiapine than placebo, with treatment effects detectable from week 1. The analysis also demonstrated increased rates of sedation, somnolence, dizziness, fatigue, constipation, dry mouth, increased appetite and weight gain. Current evidence therefore supports an important distinction between clinical efficacy and mechanistic certainty [9]. The antidepressant efficacy of quetiapine is well established, whereas the precise biological sequence through which receptor binding is translated into recovery from bipolar depression remains incompletely understood.

Pharmacokinetic Foundations of Quetiapine Pharmacology

Understanding quetiapine's mechanism requires consideration of both the parent compound and its active metabolite. Following oral administration, quetiapine is rapidly absorbed, with peak plasma concentrations occurring at approximately 1.5 hours for the immediate-release formulation. It undergoes extensive hepatic metabolism, with CYP3A4 contributing importantly to the formation of its active metabolite N-desalkylquetiapine (norquetiapine). The terminal half-life of quetiapine itself is approximately six hours [10]. The importance of CYP3A4 has direct clinical pharmacological implications. Strong CYP3A4 inhibitors can substantially increase quetiapine exposure, whereas potent CYP3A4 inducers can markedly increase their clearance. Consequently, drug interactions involving CYP3A4 can alter both the concentration of quetiapine and the pharmacological contribution of norquetiapine. The parent compound and norquetiapine should therefore be regarded as a pharmacologically related but functionally distinct pair. This is particularly important in bipolar depression because norquetiapine possesses properties that are not adequately represented by the receptor-binding profile of quetiapine itself [11].

Receptor Pharmacology of Quetiapine

Dopamine D^2 Receptor Antagonism

D^2 receptor antagonism is a defining property of antipsychotic pharmacology and contributes substantially to quetiapine's efficacy in psychotic and manic states. Quetiapine binds to dopamine D^2 receptors, although its affinity is relatively mod-

est compared with some conventional antipsychotics. Current product information reports Ki values of approximately 626 nM for quetiapine and 489 nM for norquetiapine at D^2 receptors (table 1). D^2 antagonism provides a plausible explanation for several aspects of quetiapine's clinical activity: reduction of psychotic symptoms; suppression of dopaminergically mediated manic activation; modulation of excessive mesolimbic dopamine signalling [12]. However, D^2 antagonism alone is an inadequate explanation for the antidepressant properties of quetiapine. This is an important conceptual point. If D^2 blockade were the principal mechanism responsible for antidepressant efficacy, one would expect antipsychotics with substantial D^2 antagonism to exhibit broadly similar antidepressant profiles. This is not the case. The antidepressant efficacy of quetiapine therefore appears to depend on a pharmacological profile extending beyond classical dopamine receptor antagonism (13).

Serotonin 5-HT^{2}A Receptor Antagonism

Quetiapine has substantially greater affinity for serotonin 5-HT^{2}A receptors than for D^2 receptors. Current pharmacological data report Ki values of approximately 38 nM for quetiapine and 2.9 nM for norquetiapine at 5-HT^{2}A receptors (table 1). 5-HT^{2}A antagonism is a characteristic pharmacological feature of many second-generation antipsychotics and is believed to influence the functional consequences of D^2 blockade. At the systems level, 5-HT^{2}A antagonism can facilitate dopaminergic transmission in selected cortical regions (14). This is relevant to bipolar depression because excessive reduction of cortical dopamine could theoretically worsen anhedonia, motivation and cognitive function. The serotonergic modulation produced by quetiapine may therefore permit antipsychotic dopamine regulation without producing the same degree of cortical dopaminergic suppression associated with more selective D^2 antagonism. The antidepressant significance of 5-HT^{2}A antagonism, however, should not be overstated. It is more appropriate to regard this receptor interaction as one component of a broader network of serotonergic and catecholaminergic effects (15).

Norquetiapine: the pharmacological bridge between antipsychotic and antidepressant Activity

The formation of norquetiapine represents one of the most important distinguishing characteristics of quetiapine pharmacology. Norquetiapine is not simply an inactive metabolic product. It has substantial pharmacological activity at several neurotransmitter targets and, in some cases, considerably greater affinity than quetiapine itself. For example, current pharmacological data report the following approximate Ki values for quetiapine versus norquetiapine [16]:

Target	Quetiapine	Norquetiapine
D^2	428 nM	99.8 nM
D^2	626 nM	489 nM
5-HT^{1}A	1040 nM	191 nM
5-HT^{2}A	38 nM	2.9 nM
H^1	4.4 nM	1.1 nM
M^1	1086 nM	38.3 nM
α^1B	14.6 nM	46.4 nM

Table 1 Affinity of quetiapine and norquetiapine for main brain receptors

Norepinephrine Transporter Inhibition

Norquetiapine has substantial affinity for the norepinephrine transporter (NET), whereas quetiapine itself has very low affinity for this transporter. This pharmacological difference provides one of the strongest mechanistic explanations for the antidepressant properties of quetiapine.NET normally terminates noradrenergic neurotransmission by transporting extracellular norepinephrine back into presynaptic neurons. Inhibition of NET increases extracellular norepinephrine and thereby enhances noradrenergic signalling (17). The significance of this mechanism extends beyond theoretical receptor pharmacology. Experimental studies demonstrated that norquetiapine has pharmacological activity at NET comparable with established antidepressant mechanisms, whereas quetiapine itself is comparatively inactive at NET. More importantly, human PET data provides evidence that this interaction occurs at clinically relevant exposure (18). In patients receiving quetiapine XR, NET occupancy increased with dose, and estimated quetiapine XR exposure associated with approximately 50% NET occupancy was around 256 mg/day. NET occupancy in the hypothalamus was also associated with subsequent improvement in depressive symptoms. This observation is particularly significant because it bridges three levels of evidence: quetiapine administration to norquetiapine formation to NET occupancy to association with antidepressant response. It does not prove that NET inhibition is the sole or dominant mechanism of clinical efficacy, but it substantially strengthens the hypothesis that noradrenergic modulation contributes directly to quetiapine's antidepressant effects (19).

5-HT$_1$A receptor activity

A second important property of norquetiapine is partial agonist activity at the serotonin 5-HT$_1$A receptor. 5-HT$_1$A receptors are distributed both presynaptically, where they function as autoreceptors, and postsynaptically in regions including the prefrontal cortex and hippocampus. Their activation can influence serotonin release, neuronal excitability and downstream dopaminergic and noradrenergic transmission.

Norquetiapine has greater affinity for 5-HT_1A receptors than the parent compound, and experimental work supports partial agonist activity at this receptor (18). Preclinical experiments indicate that 5-HT_1A receptor activity contributes to the anxiolytic and antidepressant-like effects of norquetiapine. This mechanism may also help explain the apparent discrepancy between quetiapine's broad receptor antagonism and its ability to improve mood. Rather than producing simple suppression of monoaminergic signalling, the parent-drug/metabolite combination produces a more complex redistribution of serotonergic, dopaminergic and noradrenergic activity.

The Integrated Monoaminergic Model

The antidepressant mechanism of quetiapine is therefore best conceptualized as a multisystem pharmacological interaction(20) .

Serotonergic Component

5-HT_2A antagonism modifies serotonergic regulation of cortical and subcortical neurotransmission, while norquetiapine's 5-HT_1A activity may facilitate antidepressant and anxiolytic signalling.

Noradrenergic Component

NET inhibition by norquetiapine increases extracellular norepinephrine and provides a pharmacological mechanism resembling, in part, conventional noradrenergic antidepressant treatment.

Dopaminergic Component

5-HT_2A antagonism and 5-HT_1A-mediated effects may increase dopaminergic signalling in selected cortical regions, while D_2 antagonism regulates excessive mesolimbic dopaminergic activity. The result is not simply "more dopamine" or "less dopamine." Rather, quetiapine appears to redistribute monoaminergic signalling according to brain region and receptor context. This regional pharmacology may be particularly relevant to bipolar disorder, in which excessive dopaminergic activity is associated with mania while deficient motivational and reward-related signalling may contribute to depressive symptoms (21).

α_1-Adrenergic and α_2-Adrenergic pharmacology

Quetiapine and norquetiapine interact with adrenergic receptors, although their affinities differ. α_1-adrenergic antagonism has an important clinical consequence: vasodilation and impaired compensatory vasoconstriction can produce orthostatic hypotension, particularly during initial treatment and rapid titration (22). The product label specifically attributes orthostatic hypotension in part to α_2 antagonism. Norquetiapine also interacts with α_2-adrenergic receptors. Experimental studies suggest that α_2 receptor modulation can increase noradrenergic neuronal firing and contribute to enhanced noradrenergic transmission. Norquetiapine had distinctive properties which may depend on its ability to inhibit norepinephrine transporter and involve β2/α2 adrenergic receptors. (23). This provides a second potential pathway through which quetiapine may enhance noradrenergic function in addition to direct NET inhibition. The distinction is mechanistically relevant: NET inhibition prolongs the action of released norepinephrine, whereas modulation of presynaptic α_2 receptors can influence the amount of norepinephrine released in the first place. The combination could therefore amplify noradrenergic signalling through both presynaptic and reuptake mechanisms.

5-HT_2C and 5-HT_7 receptors

Norquetiapine has also been reported to antagonize 5-HT_2C and 5-HT_7 receptors. These interactions have been proposed as additional contributors to antidepressant activity. 5-HT_2C receptors regulate serotonergic, dopaminergic and noradrenergic neurotransmission. Their antagonism may facilitate catecholaminergic transmission in cortical regions and could therefore complement NET inhibition and 5-HT_1A activity.5-HT_7 receptors are implicated in mood regulation, cognition and circadian processes (16). Quetiapine's interaction with this receptor has generated hypotheses concerning downstream effects on intracellular signalling and metabolic pathways, but the clinical relevance of these mechanisms remains considerably less certain than the evidence supporting D_2/5-HT_2A interactions or NET inhibition. Consequently, these mechanisms should be regarded as potential contributors, rather than established explanations of clinical efficacy.

Histamine H_1 receptor antagonism

Both quetiapine and norquetiapine have high affinity for histamine H_1 receptors (table 1). H_1 antagonism explains an important component of quetiapine's sedative properties . Sedation is particularly prominent during treatment initiation and may be clinically advantageous when insomnia, agitation or anxiety accompanies bipolar depression. However, sedation is also a major limitation. Excessive daytime somnolence can impair functioning, driving safety and adherence. H_1antagonism may also contribute to increased appetite and subsequent weight gain (24). Therefore, the same receptor interaction that may provide symptomatic benefit through sleep normalization can contribute to a clinically important adverse-effect burden.

Muscarinic receptors: an important correction to older descriptions

An important point when revisiting older descriptions of quetiapine pharmacology concerns muscarinic activity. Older lit-

erature sometimes characterizes quetiapine as having little clinically meaningful cholinergic activity. Contemporary product information provides a more nuanced picture: the parent drug has relatively low affinity for muscarinic M_1 receptors, whereas norquetiapine has substantially greater affinity. This distinction is clinically relevant because norquetiapine-associated muscarinic antagonism may contribute to dry mouth, constipation and other anticholinergic effects (25). Thus, descriptions of quetiapine as having essentially "no cholinergic activity" are overly simplistic when the pharmacology of the active metabolite is considered.

From receptor pharmacology to clinical antidepressant action

The key pharmacological question is how the molecular profile described above improves bipolar depression. One useful model is that quetiapine antagonizes 5-HT_2A receptors, thereby modulating cortical dopaminergic and serotonergic signalling, while norquetiapine inhibits NET, increases extracellular norepinephrine, and acts as a partial 5-HT_1A agonist to influence serotonergic and cortical dopaminergic networks. Together, these actions may affect mood, anxiety, motivation, cognition, and sleep (26). This integrated model fits quetiapine's clinical pharmacology better than the traditional explanation based solely on D_2 antagonism. However, current evidence does not support a single linear molecular pathway; the antidepressant response likely arises from several concurrent pharmacodynamic processes across distinct neural circuits.

Evidence for additional intracellular and neuroplastic mechanisms

Several studies have investigated whether quetiapine affects intracellular signalling pathways associated with neuroplasticity, including ERK/MAPK, PI3K/Akt, BDNF-related pathways and GSK-3 signalling (27). These pathways are biologically plausible because neuroplasticity, synaptic remodelling and intracellular signalling are increasingly implicated in the pathophysiology of mood disorders. However, evidence for these mechanisms should be interpreted cautiously. For example, computational and network-pharmacology studies have identified potential interactions between quetiapine and signalling pathways involving BDNF, PI3K/Akt and MAPK. Such findings may generate useful mechanistic hypotheses but do not demonstrate that these pathways mediate clinical antidepressant efficacy in humans (28).Similarly, GSK-3β has substantial biological relevance to bipolar disorder, but evidence linking quetiapine's clinical efficacy directly to therapeutically meaningful GSK-3β inhibition is considerably weaker than the evidence for lithium and other agents acting on this pathway (29). Therefore, intracellular signalling should currently be considered a secondary mechanistic hypothesis, not an established primary mechanism of quetiapine.

Circadian and sleep-related effects

Sleep and circadian disruption are central components of bipolar disorder (30). Quetiapine's strong H_1 antagonism produces sedation and changes sleep architecture, while experimental and clinical studies suggest that quetiapine can influence circadian parameters. In patients with bipolar II depression, quetiapine XR and lithium produced changes in actigraphy-derived circadian measures, although their effects were not identical (31). It is tempting to interpret these observations as evidence that circadian normalization mediates antidepressant efficacy. However, the direction of causality remains uncertain. Sedation may improve sleep secondary to H_1 antagonism without directly correcting the molecular circadian abnormalities underlying bipolar disorder. Consequently, the relationship between quetiapine, sleep, circadian rhythms and mood remains an important area for further research.

Clinical efficacy in acute bipolar depression

The efficacy of quetiapine in acute bipolar depression is among the most reproducible findings in contemporary psychopharmacology. The pivotal trials generally evaluated 300 and 600 mg/day. Both doses were superior to placebo, but the higher dose did not consistently provide additional antidepressant benefit. The current prescribing information summarizes two major eight-week trials involving 1,045 patients with bipolar I or II depression. Quetiapine 300 and 600 mg/day were both superior to placebo, with improvement evident from approximately day 8, and no additional benefit from 600 mg/day over 300 mg/day (32,33). This dose-response relationship is pharmacologically interesting. If antidepressant efficacy were determined simply by increasing D_2 receptor blockade, one might anticipate greater efficacy at 600 mg/day. Instead, the clinical data suggest that the antidepressant response reaches a plateau at approximately 300 mg/day in many patients. One possible explanation is that clinically important antidepressant targets including NET and 5-HT_1A systems reach sufficient engagement at relatively moderate exposure, whereas increasing the dose may disproportionately increase receptor-mediated adverse effects such as sedation and orthostatic hypotension (34). A network meta-analysis comparing immediate-release and extended-release formulations found no significant efficacy difference between quetiapine 300 mg/day, quetiapine 600 mg/day and quetiapine XR 300 mg/day, further supporting the absence of a consistent dose-related antidepressant advantage above 300 mg/day (35).

Bipolar I versus Bipolar II depression

Quetiapine is unusual in having substantial evidence across

both bipolar I and bipolar II depression. Pooled analyses of randomized trials demonstrate efficacy in bipolar II depression, although individual bipolar II studies have sometimes been underpowered (36). Current CANMAT/ISBD recommendations place quetiapine as a first-line treatment for bipolar II depression and as a first-line option for bipolar I depression. This broad efficacy may reflect the fact that the depressive phase of bipolar disorder shares several neurobiological substrates across bipolar I and II disorders, even though the phenomenology and lifetime course differ .

Antimanic effects

Quetiapine is also an established treatment for acute mania. The mechanistic basis of antimanic efficacy is more straightforward than the antidepressant mechanism. D_2 receptor antagonism, together with serotonergic modulation, provides a plausible explanation for reduction of excessive dopaminergic signalling associated with mania (37) . However, the precise molecular mechanism underlying mood stabilization remains incompletely established. Contemporary reviews emphasize that preclinical models of bipolar mania are limited and that mechanistic evidence for the antimanic effects of quetiapine is less developed than evidence concerning its antidepressant pharmacology (38). This distinction is important: the mechanistic model of quetiapine should not imply that the same molecular process explains depression and mania in opposite directions. Instead, quetiapine may exert different functional consequences in different neural circuits, with D_2 antagonism particularly relevant to excessive dopaminergic activity during mania and the norquetiapine-mediated serotonergic/noradrenergic effects contributing substantially to antidepressant efficacy.

Maintenance treatment and relapse prevention

Quetiapine has also demonstrated efficacy in maintenance treatment. In a large, randomized maintenance trial, patients stabilized on quetiapine were randomized to continued quetiapine, lithium or placebo. Continued quetiapine significantly prolonged the time to recurrence of any mood event compared with placebo and reduced both manic and depressive recurrences (39). Combination treatment with lithium or divalproex has also demonstrated substantial relapse-prevention efficacy. In a large trial, continued quetiapine plus lithium or divalproex reduced the risk of recurrence of any mood event, with significant reductions in both manic and depressive events (40). A particularly important interpretation is that quetiapine's maintenance effect cannot be reduced to prevention of mania. Its ability to reduce depressive recurrence is clinically important and is consistent with the drug's antidepressant pharmacology. Nevertheless, maintenance studies require careful interpretation because many were conducted using an enriched design: patients had to respond to quetiapine during an open-label stabilization phase before randomization. This design can overestimate effectiveness in an unselected clinical population (41,42).

Adverse effects because of receptor pharmacology

The adverse effect profile of quetiapine can be understood to a substantial degree from its receptor interactions. H_1 antagonism associated principally with sedation; somnolence; increased appetite; weight gain.α_1-adrenergic antagonism associated principally with orthostatic hypotension; dizziness; reflex tachycardia in susceptible individuals. Muscarinic antagonism, particularly through norquetiapine associated with dry mouth; constipation; impaired gastrointestinal motility; other anticholinergic effects. Dopamine D_2 antagonism can contribute to extrapyramidal symptoms; akathisia; hyperprolactinemia, although generally less prominently than with stronger D_2 antagonists.Metabolic effects like weight gain and disturbances of glucose and lipid metabolism represent clinically important limitations of quetiapine therapy (43).
These effects are not adequately explained by a single receptor. H_1 antagonism, metabolic signalling and broader central and peripheral effects may all contribute. Clinical trials consistently demonstrate a higher burden of somnolence and weight gain compared with placebo. The contemporary product label also emphasizes metabolic and cardiovascular monitoring and identifies orthostatic hypotension, somnolence and metabolic abnormalities among important safety considerations (44).

Clinical pharmacology and dose selection

For acute adult bipolar depression, the immediate-release formulation is conventionally titrated rapidly from 50 mg at bedtime to 300 mg/day over four days according to the product label. The clinical pharmacology of quetiapine makes gradual titration particularly relevant because H_1 and α_1 receptor antagonism can produce prominent sedation and orthostatic effects before tolerance develops. The relationship between dose and therapeutic response is therefore not linear (45). Increasing the dose may increase exposure to D_2 and other receptors without proportionally improving antidepressant efficacy. This is one reason why the commonly studied 300 mg/day dose has become pharmacologically and clinically important in bipolar depression. The extended-release formulation can provide a different pharmacokinetic profile and may offer practical advantages in some patients, but available comparative evidence does not establish a major antidepressant efficacy advantage over immediate-release treatment at clinically relevant doses (46).

Drug–drug interactions

The CYP3A4 dependence of quetiapine metabolism is highly relevant to clinical pharmacology. Strong CYP3A4 inhibitors can markedly increase quetiapine exposure, while strong

CYP3A4 inducers can substantially increase clearance (47). The current prescribing information recommends major dose modification when potent inhibitors or inducers are coadministered. This is particularly relevant in bipolar disorder because patients may receive complex polypharmacy involving anticonvulsants, antidepressants, cardiovascular medications and other psychotropic drugs .Carbamazepine, for example, is a potent CYP3A4 inducer and can substantially lower quetiapine exposure. Conversely, potent CYP3A4 inhibitors can markedly increase exposure and thereby intensify sedation, hypotension and other concentration-dependent effects (48). The interaction between pharmacokinetics and norquetiapine formation also means that drug interactions may potentially alter not only the absolute concentration of quetiapine but the relative contribution of the metabolite to clinical pharmacology (49).

A critical appraisal of the mechanism of action

The evidence supports a hierarchical model of mechanistic certainty.

- **Well established:** quetiapine antagonizes D_2 receptors; quetiapine antagonizes 5-HT_2A receptors; quetiapine and norquetiapine interact with H1 and α1 receptors; norquetiapine has substantial activity at NET; norquetiapine interacts with 5-HT_1A receptors; quetiapine is clinically effective in bipolar depression; clinically relevant NET occupancy has been demonstrated in humans (50).

- **Strongly supported but not sufficient as a complete explanation:** NET inhibition contributes to antidepressant activity; 5-HT_1A activity contributes to antidepressant and anxiolytic effects; serotonergic modulation facilitates regional dopaminergic signalling; the parent-drug/metabolite combination produces complementary monoaminergic effects (18).

- **Plausible but incompletely established :** BDNF-related neuroplasticity; ERK/MAPK and PI3K/Akt signalling; GSK-3β modulation; circadian-clock effects; immune and inflammatory mechanisms; HCN-channel effects (27).

This hierarchy is important because pharmacological reviews frequently make an implicit transition from binding affinity to clinical mechanism. These are not equivalent. A drug can bind a receptor in vitro without that receptor being occupied to a clinically relevant extent in humans. Similarly, receptor occupancy does not establish that interaction is necessary for therapeutic efficacy. The most convincing mechanistic evidence for quetiapine's antidepressant activity therefore comes from convergence between receptor/transporter pharmacology, clinically achievable concentrations, human imaging data, preclinical functional studies and randomized clinical trials (51).

Clinical Implications

From a clinical pharmacology perspective, quetiapine's major advantage is that a single agent can provide clinically meaningful antidepressant and antimanic effects while also having evidence for maintenance treatment (38). Current CANMAT/ISBD recommendations place quetiapine among the leading treatments for acute bipolar depression and maintenance. However, treatment selection must balance efficacy against adverse effects. Quetiapine may be particularly attractive when bipolar depression coexists with significant anxiety ; insomnia; agitation; previous psychotic symptoms; a history of manic episodes requiring antipsychotic treatment a need for an agent with evidence across several phases of illness (52). Conversely, substantial obesity, diabetes, dyslipidemia, excessive daytime sedation, orthostatic vulnerability or significant anticholinergic burden may make alternative treatments preferable. Thus, the pharmacological profile of quetiapine is simultaneously its principal strength and its principal limitation: the same broad receptor activity responsible for its therapeutic versatility also generates a substantial adverse-effect burden.

Limitations of the Current Mechanistic Evidence

Despite extensive investigation, several major questions remain unresolved. First, no single receptor interaction fully explains the clinical antidepressant effect. Second, much of the mechanistic evidence derives from in vitro studies or animal models, which cannot fully reproduce human bipolar disorder. Third, bipolar depression is biologically heterogeneous. The mechanisms contributing to anhedonia, anxiety, psychomotor retardation, insomnia and cognitive dysfunction may differ substantially between individuals. Fourth, receptor affinity does not necessarily correspond to receptor occupancy at therapeutic concentrations. Fifth, the relationship between norquetiapine exposure and clinical response requires further investigation. The PET evidence for NET occupancy is compelling but remains preliminary with respect to causality. Finally, the maintenance effects of quetiapine cannot necessarily be extrapolated directly from its acute antidepressant mechanism. Long-term relapse prevention may involve adaptation of neural networks and behavioural/circadian systems that are not captured by short-term receptor pharmacology (53).

Conclusion

Quetiapine is best understood not as a conventional dopamine antagonist with secondary antidepressant properties, but as a multimodal neuropharmacological agent whose clinical effects emerge from the combined actions of quetiapine and its active metabolite norquetiapine. D_2 and 5-HT_2A

receptor antagonism provides an important pharmacological basis for antipsychotic and antimanic efficacy. However, the antidepressant effects of quetiapine are more plausibly explained by the interaction of serotonergic, noradrenergic and dopaminergic mechanisms. Of particular importance is norquetiapine, which inhibits the norepinephrine transporter and exhibits 5-HT_1A partial agonist activity. Human PET studies demonstrating clinically relevant NET occupancy provide an important translational link between the pharmacology of norquetiapine and antidepressant efficacy. At the same time, quetiapine's broad receptor activity accounts for many of its clinically important adverse effects. H_1 antagonism contributes to sedation and appetite stimulation, α_1 antagonism contributes to orthostatic hypotension, and muscarinic activity particularly that of norquetiapine contributes to anticholinergic adverse effects. Weight gain and metabolic abnormalities remain important limitations to long-term treatment. It is a “dirty drug” which is an informal term for a drug that acts on multiple receptors or biological targets, rather than being highly selective for one target. The clinical evidence establishes quetiapine as an effective treatment for acute bipolar depression and as an important maintenance agent. Nevertheless, the molecular mechanism responsible for its antidepressant and mood-stabilizing effects remains incompletely resolved. The strongest contemporary model is therefore one of integrated multimodal pharmacology, in which D_2/5-HT_2A antagonism, noradrenergic transporter inhibition, 5-HT_1A activity and broader receptor-network effects interact across brain regions to produce therapeutic effects on both poles of bipolar illness. The most important conceptual advance is consequently the recognition that the pharmacology of quetiapine cannot be adequately understood by studying quetiapine alone. Norquetiapine is pharmacologically active, reaches clinically relevant concentrations, occupies therapeutically relevant targets and probably contributes substantially to the antidepressant phenotype. Understanding this parent-drug/metabolite relationship is central to explaining why quetiapine occupies a distinctive position in the pharmacotherapy of bipolar depression.

References

1. Bourin, Michel. "The Diagnosis of Bipolar Disorders: A Major Public Health Issue." Alpha Psychiatry 25, no. 6 (2024): 750.
2. Menon, Vikas, Ragul Ganesh, Raman Deep, Sujit Sarkhel, Santanu Goswami, Debadatta Mohapatra, Ravindra Neelakanthappa Munoli, Podila Satya Venkata Narasimha Sharma, M. S. Reddy, and Kesavan Muralidharan. "Clinical practice guidelines for the management of bipolar disorder: 2025 update." Indian Journal of Psychiatry 68, no. 1 (2026): 8.
3. Bourin, M. "Are antidepressants useful in bipolar disease." Arch Depress Anxiety 3, no. 2 (2017): 058-059.
4. Keramatian, Kamyar, Nellai K. Chithra, and Lakshmi N. Yatham. "The CANMAT and ISBD guidelines for the treatment of bipolar disorder: summary and a 2023 update of evidence." Focus 21, no. 4 (2023): 344-353.
5. Soeiro-de-Souza, Márcio G., Vasco Videira Dias, Giovanni Missio, Vicent Balanzá-Martinez, Leandro Valiengo, Andre F. Carvalho, and Ricardo Alberto Moreno. "Role of quetiapine beyond its clinical efficacy in bipolar disorder: From neuroprotection to the treatment of psychiatric disorders." Experimental and therapeutic medicine 9, no. 3 (2015): 643-652.
6. Brugue, Esteve, and Eduard Vieta. "Atypical antipsychotics in bipolar depression: neurobiological basis and clinical implications." Progress in Neuro-Psychopharmacology and Biological Psychiatry 31, no. 1 (2007): 275-282.
7. Thase, Michael E., Wayne Macfadden, Richard H. Weisler, William Chang, Björn Paulsson, Arifulla Khan, Joseph R. Calabrese, and Bolder II Study Group. "Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study)." Journal of clinical psychopharmacology 26, no. 6 (2006): 600-609.
8. McElroy, Susan L., Richard H. Weisler, William Chang, Bengt Olausson, Björn Paulsson, Martin Brecher, Vasavan Agambaram, Charles Merideth, Arvid Nordenhem, and Allan H. Young. "A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II)." Journal of Clinical Psychiatry 71, no. 2 (2010): 163.
9. Suttajit, Sirijit, Manit Srisurapanont, Narong Maneeton, and Benchalak Maneeton. "Quetiapine for acute bipolar depression: a systematic review and meta-analysis." Drug design, development and therapy (2014): 827-838.
10. DeVane, C. Lindsay, and Charles B. Nemeroff. "Clinical pharmacokinetics of quetiapine: an atypical antipsychotic." Clinical pharmacokinetics 40, no. 7 (2001): 509-522.
11. Krejčí, Veronika, Irena Murínová, Ondřej Slanař, and Martin Šíma. "Evidence for therapeutic drug monitoring of atypical antipsychotics." Prague Medical Report 125, no. 2 (2024): 101-129.
12. Nord, Magdalena, Svante Nyberg, Jacob Brogren, Aurelija Jucaite, Christer Halldin, and Lars Farde. "Comparison of D2 dopamine receptor occupancy after oral administration of quetiapine fumarate immediate-release and extended-release formulations in healthy subjects." International Journal of Neuropsychopharmacology 14, no. 10 (2011): 1357-1366.
13. Grinchii, Daniil, and Eliyahu Dremencov. "Mechanism of action of atypical antipsychotic drugs in mood disorders." International Journal of Molecular Sciences 21, no. 24 (2020): 9532.
14. Gefvert, Ola, Tommie Lundberg, Marie Wieselgren, Mats Bergström, Bengt Långström, Frits-Axel Wiesel, and Leif Lindström. "D2 and 5HT2A receptor occupancy of different doses of quetiapine in schizophrenia: a PET study." European Neuropsychopharmacology 11, no. 2 (2001): 105-110.

15. Prieto, E., J. A. Micó, J. J. Meana, and S. Majadas. "Neurobiological bases of quetiapine antidepresant effect in the bipolar disorder." Actas Españolas de Psiquiatría 38, no. 1 (2010): 22-32.
16. Cross, A. J., D. Widzowski, C. Maciag, A. Zacco, T. Hudzik, J. Liu, S. Nyberg, and M. W. Wood. "Quetiapine and its metabolite norquetiapine: translation from in vitro pharmacology to in vivo efficacy in rodent models." British journal of pharmacology 173, no. 1 (2016): 155-166.
17. Nyberg, Svante, Aurelija Jucaite, Akihiro Takano, Matts Kågedal, Zsolt Cselényi, Christer Halldin, and Lars Farde. "Norepinephrine transporter occupancy in the human brain after oral administration of quetiapine XR." International Journal of Neuropsychopharmacology 16, no. 10 (2013): 2235-2244.
18. López-Muñoz, Francisco, and Cecilio Álamo. "Active metabolites as antidepressant drugs: the role of norquetiapine in the mechanism of action of quetiapine in the treatment of mood disorders." Frontiers in psychiatry 4 (2013): 102.
19. Yatham, Lakshmi N., Vesna Sossi, Yu-Shin Ding, Nasim Vafai, Shyam Sundar Arumugham, Taj Dhanoa, Raymond W. Lam, David J. Bond, and Joseph H. Puyat. "A positron emission tomography study of norepinephrine transporter occupancy and its correlation with symptom response in depressed patients treated with quetiapine XR." International Journal of Neuropsychopharmacology 21, no. 2 (2018): 108-113.
20. Daly, Ella J., and Madhukar H. Trivedi. "A review of quetiapine in combination with antidepressant therapy in patients with depression." Neuropsychiatric Disease and Treatment 3, no. 6 (2007): 855-867.
21. Ichikawa, Junji, Hideo Ishii, Stefania Bonaccorso, Wiley L. Fowler, Ian A. O'Laughlin, and Herbert Y. Meltzer. "5-HT2A and D2 receptor blockade increases cortical DA release via 5-HT1A receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release." Journal of neurochemistry 76, no. 5 (2001): 1521-1531.
22. Stanford, S. Clare, and David J. Heal. "Adrenoceptors: a focus on psychiatric disorders and their treatments." Adrenoceptors (2023): 507-554.
23. Bortolotto, Valeria, Pier Luigi Canonico, and Mariagrazia Grilli. "β2 and α2 adrenergic receptors mediate the proneurogenic in vitro effects of norquetiapine." Neural Regeneration Research 16, no. 10 (2021): 2041.
24. Modesto-Lowe, Vania, Agata K. Harabasz, and Sophia A. Walker. "Quetiapine for primary insomnia: Consider the risks." Cleveland Clinic Journal of Medicine 88, no. 5 (2021): 286-294.
25. Goldstein, Jeffrey. "Clarification of anticholinergic effects of quetiapine." The Journal of Clinical Psychiatry (2000).
26. Sanford, Mark, and Gillian M. Keating. "Quetiapine: a review of its use in the management of bipolar depression." CNS drugs 26, no. 5 (2012): 435-460.
27. Lan, Yanping, Ao Li, Chenzhe Ding, Jianxue Xia, Xuebing Zhang, and Dongyang Luo. "Mechanistic insights into Quetiapine's Protective effects on cognitive function and synaptic plasticity in epileptic rats." Brain Research 1850 (2025): 149426.
28. Li, Chao, Hongjun Tian, Ranli Li, Feng Jia, Lina Wang, Xiaoyan Ma, Lei Yang et al. "Molecular mechanisms of quetiapine bidirectional regulation of bipolar depression and mania based on network pharmacology and molecular docking: evidence from computational biology." Journal of affective disorders 355 (2024): 528-539.
29. Costemale-Lacoste, J. F., J. P. Guilloux, and R. Gaillard. "The role of GSK-3 in treatment-resistant depression and links with the pharmacological effects of lithium and ketamine: A review of the literature." L'encephale 42, no. 2 (2016): 156-164.
30. Tonon, André C., Adile Nexha, Mariana Mendonça da Silva, Fabiano A. Gomes, Maria Paz Hidalgo, and Benicio N. Frey. "Sleep and circadian disruption in bipolar disorders: From psychopathology to digital phenotyping in clinical practice." Psychiatry and clinical neurosciences 78, no. 11 (2024): 654-666.
31. Gedge, Laura, Lauren Lazowski, David Murray, Ruzica Jokic, and Roumen Milev. "Effects of quetiapine on sleep architecture in patients with unipolar or bipolar depression." Neuropsychiatric Disease and Treatment (2010): 501-508.
32. Calabrese, Joseph R., Paul E. Keck Jr, Wayne Macfadden, Margaret Minkwitz, Terence A. Ketter, Richard H. Weisler, Andrew J. Cutler et al. "A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression." American Journal of Psychiatry 162, no. 7 (2005): 1351-1360.
33. Thase, Michael E., Wayne Macfadden, Richard H. Weisler, William Chang, Björn Paulsson, Arifulla Khan, Joseph R. Calabrese, and Bolder II Study Group. "Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study)." Journal of clinical psychopharmacology 26, no. 6 (2006): 600-609.
34. Bauer, Michael, Herman W. Pretorius, Eric L. Constant, Willie R. Earley, Johan Szamosi, and Martin Brecher. "Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study." Journal of Clinical Psychiatry 70, no. 4 (2009): 540.
35. Bauer, Michael, Nizar El-Khalili, Catherine Datto, Johan Szamosi, and Hans Eriksson. "A pooled analysis of two randomised, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder." Journal of affective disorders 127, no. 1-3 (2010): 19-30.
36. Thase, Michael E. "Quetiapine monotherapy for bipolar depression." Neuropsychiatric disease and treatment 4, no. 1 (2008): 21-31.

37. McIntyre, Roger S., Miriam Cohen, Jun Zhao, Larry Alphs, Thomas A. Macek, and John Panagides. "Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial." Journal of affective disorders 122, no. 1-2 (2010): 27-38.
38. Miranda, Aline Silva de, Fabrício A. Moreira, and Antônio Lúcio Teixeira. "The preclinical discovery and development of quetiapine for the treatment of mania and depression." Expert Opinion on Drug Discovery 12, no. 5 (2017): 525-535.
39. Weisler, Richard H., Willem A. Nolen, Anders Neijber, Åsa Hellqvist, and Björn Paulsson. "Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder (Trial 144: a randomized controlled study)." Journal of Clinical Psychiatry 72, no. 11 (2011): 1452.
40. Vieta, Eduard, Trisha Suppes, Ivan Eggens, Inger Persson, Björn Paulsson, Martin Brecher, and Trial 126 Study Investigators. "Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126)." Journal of affective disorders 109, no. 3 (2008): 251-263.
41. Lindström, Leif, Eva Lindström, Mikael Nilsson, and Malin Höistad. "Maintenance therapy with second generation antipsychotics for bipolar disorder–a systematic review and meta-analysis." Journal of Affective Disorders 213 (2017): 138-150.
42. Sanford, Mark, and Gillian M. Keating. "Quetiapine: a review of its use in the management of bipolar depression." CNS drugs 26, no. 5 (2012): 435-460.
43. Dev, Vikram, and Joher Raniwalla. "Quetiapine: a review of its safety in the management of schizophrenia." Drug safety 23, no. 4 (2000): 295-307.
44. Sonim, Pedro, Rui M. Ferreira, Inês Lourenço, Lia Fernandes, and Ana Rita Ferreira. "Metabolic Adverse Effects of Low-Dose Quetiapine: A Systematic Review and Meta-Analysis." Acta Psychiatrica Scandinavica 152, no. 5 (2025): 328-340.
45. Sanford, Mark, and Gillian M. Keating. "Quetiapine: a review of its use in the management of bipolar depression." CNS drugs 26, no. 5 (2012): 435-460.
46. El-Khalili, Nizar. "Update on extended release quetiapine fumarate in schizophrenia and bipolar disorders." Neuropsychiatric Disease and Treatment (2012): 523-536.
47. Bakken, Gry Vibeke, Ida Rudberg, Hege Christensen, Espen Molden, Helge Refsum, and Monica Hermann. "Metabolism of quetiapine by CYP3A4 and CYP3A5 in presence or absence of cytochrome B5." Drug metabolism and disposition 37, no. 2 (2009): 254-258.
48. Jang, Ji-Hun, and Seung-Hyun Jeong. "Physiologically based pharmacokinetic framework for predicting CYP3A4-mediated drug–drug interactions of quetiapine with ketoconazole and carbamazepine." Drug Metabolism and Disposition (2026): 100356.
49. Joshi, Kalpesh, Sameer Rao, and Suyog Mehta. "A review of pharmacokinetic and pharmacodynamic properties of quetiapine IR and XR: Insights and clinical practice implications." Cureus 17, no. 6 (2025).
50. Pira, Luigi, Raymond Mongeau, and Luca Pani. "The atypical antipsychotic quetiapine increases both noradrenaline and dopamine release in the rat prefrontal cortex." European journal of pharmacology 504, no. 1-2 (2004): 61-64.
51. Muneer, Ather. "Pharmacotherapy of bipolar disorder with quetiapine: a recent literature review and an update." Clinical Psychopharmacology and Neuroscience 13, no. 1 (2015): 25.
52. Koshy, Rowyna Reji, Pramodhiya Sanduni Perera, Aleena Jaxon, Reeves Thomas George, Amal Augusthy, and Dino Stephen Thomas. "Quetiapine in psychiatric practice: A narrative review on clinical efficacy, cardiac safety, and emerging therapeutic innovations." Archives of Biological Psychiatry (2026).
53. Moreines, Jared L., Zoe L. Owrutsky, Kimberly G. Gagnon, and Anthony A. Grace. "Divergent effects of acute and repeated quetiapine treatment on dopamine neuron activity in normal vs. chronic mild stress induced hypodopaminergic states." Translational Psychiatry 7, no. 12 (2017): 1275.

Citation: Michel Bourin. Quetiapine in bipolar disorder: clinical pharmacology, receptor pharmacology, and the mechanistic basis of its antidepressant and mood-stabilizing effects. *J. Psychiatry. Psychiatr. Disord.* Vol. 5 Iss. 2. (2026) DOI: 10.58489/2836-3558/048