

New developments in the management of major depressive disorder and generalized anxiety disorder: role of quetiapine

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Abstract: Quetiapine has demonstrated efficacy in schizophrenia, bipolar disorder and in the treatment of specific symptom clusters such as agitation and sleep problems in mood disorders. In this review, randomized controlled studies demonstrating efficacy, safety and tolerability of quetiapine in major depressive disorder (MDD) and general anxiety disorder (GAD) are evaluated. The results show that quetiapine monotherapy and quetiapine augmentation of antidepressant treatment in MDD and GAD are efficacious for short-term and maintenance treatment at a dose range between 50 and 300 mg/day. Quetiapine appears to have a specific but overall mild side-effect profile, though, some adverse effects such as sedation and somnolence may lead to withdrawal from treatment in some patients. Overall, the available evidence suggests that there is a significant role for quetiapine in the treatment of MDD and GAD.

Keywords: quetiapine, major depressive disorders, general anxiety disorder, randomized controlled studies, adverse effects

Introduction

The enhancement of treatment response of major depressive disorder (MDD) and general anxiety disorder (GAD) is a major goal in clinical research and patient care. Clinical trials indicate that over 50% of depressed patients show an inadequate response to antidepressant therapy (Fava and Davidson 1996; Ferrier 1999) and that incomplete recovery from MDD increases the risk of both chronicity and recurrence. Recovery, which involves a complete remission of symptoms and a return to baseline psychosocial function, should be the goal of therapy (Rush and Trivedi 1995; Nierenberg and Wright 1999). Poor response to adequate antidepressant treatment has been termed 'treatment resistant depression' (TRD) (Ananth 1998). Although there is lack of agreement on a formal definition of TRD, one that is often cited defines it as a failure of response to at least two trials of antidepressant medication, at an adequate dose and duration from at least two different classes (Ananth 1998). Issues such as adherence, missed diagnosis of psychotic depression, bipolar disorder, or co-morbid anxiety should be investigated in patients who have not responded to initial therapeutic strategies (Kennedy and Lam 2003).

Beyond ensuring optimal use of the index antidepressant, treatment strategies for TRD include switching to another antidepressant, and augmentation or combination with two or more agents. In patients with TRD, adding or augmenting with lithium, tri-iodothyronine or atypical antipsychotics have demonstrated benefits (Kennedy and Lam 2003). Augmentation with atypical antipsychotics, including risperidone, olanzapine, ziprasidone, and quetiapine, has shown promising results in terms of improving remission rates (Shelton and Papakostas 2008).

The atypical antipsychotic quetiapine has shown efficacy in the treatment of positive and negative symptoms in schizophrenia (Srisurapanont et al 2004).

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Quetiapine has more recently gained attention as a clinically useful treatment option in patients with bipolar affective disorder (Calabrese et al 2005; Thase et al 2006; Keating and Robinson 2007; Weisler et al 2008b) and major depression (Todder et al 2006; Baune et al 2007) due to its mood stabilizing effects (Ghaemi and Katzow 1999; Vieta 2005).

Quetiapine and its major active human plasma metabolite, N-desalkyl quetiapine, has shown in vitro antagonistic activity on multiple brain neurotransmitter receptors and in particular on serotonergic (5HT_{2A}), noradrenergic (α_1 -adrenoreceptor) and the noradrenergic transporter, thus having a positive influence on mood (Arango and Bernardo 2005). With its anti-dopaminergic properties (D₁, D₂), quetiapine is considered to evolve impact on motor activity, eg, on agitation in depression (Todder et al 2006; Dannlowski et al in press).

Quetiapine has demonstrated clinical efficacy in the past few years for clinical indications ranging from bipolar disorder (Berk and Dodd 2005; Calabrese et al 2005; Croissant et al 2006) and treatment of behavioral disturbances in dementia (Savaskan et al 2006) to the management of substance dependence disorders (Sattar et al 2004; Croissant et al 2006; Hanley and Kenna 2008). Moreover, positive effects of quetiapine on sleep architecture and sleep recovery in healthy subjects (Cohrs et al 2004) as well as its sleep promoting effects in depression (Todder et al 2006) and bipolar disorder (Sokolski and Denson 2003), have been demonstrated in recent years. Preliminary evidence suggests a role for quetiapine in managing TRD (Sagud et al 2006; Doree et al 2007) and anxiety symptoms in bipolar depression (Hirschfeld et al 2006).

These recently published studies support the view that quetiapine has a broad range of clinical use in mood disorders including major depression and symptom clusters such as agitation and sleep deterioration in mood and anxiety disorders. Although a number of reviews have examined the efficacy of quetiapine in bipolar disorder (Dando and Keating 2005; Keating and Robinson 2007; Khazaal et al 2007; Shelton and Papakostas 2008), there is no review of controlled randomized studies in MDD and GAD available to date. Most recent accumulating data on the effects of quetiapine in MDD and anxiety disorder have been substantially derived from small open-label uncontrolled studies (Philip et al 2008), since data from randomized controlled studies were not available, such as for quetiapine as augmentation therapy for depression or anxiety (Nemeroff 2005).

A review of randomized and controlled studies focusing on the efficacy, safety and tolerability, and patient outcomes, such as quality of life, patient satisfaction and adherence for quetiapine treatment of MDD and GAD, would be of use to the clinical and research orientated reader. This review evaluates the recently available randomized controlled studies on quetiapine in MDD and GAD (Philip et al 2008) and goes beyond the mostly open-label studies published on quetiapine in TRD or unipolar depression (Nemeroff 2005; Gao et al 2006; Doree et al 2007).

Method

Studies were identified using searches of Pubmed/Medline. Searches were conducted by cross-referencing the term 'major depressive disorder (MDD)' or 'general anxiety disorder (GAD)' with 'quetiapine'. Restriction to the minimum criteria of double-blind, randomized, placebo controlled studies published in the English language was used. These searches were then repeated using EMBase and the Cochrane databases as well. We also searched the abstracts of major psychiatric meetings held since 2000 (American Psychiatric Association; New Clinical Drug Evaluation Unit of the National Institutes of Mental Health; American College of Neuropsychopharmacology; European College of Neuropsychopharmacology; Collegium Internationale Neuropsychopharmacologicum; Society of Biological Psychiatry, World Federation of Societies of Biological Psychiatry; World Psychiatric Association).

Results

Pharmacology of immediate and extended release quetiapine Rationale and mode of action

The receptor-binding properties of quetiapine are complex, and it appears unlikely that a single mechanism could explain the observed influence on major depression and anxiety disorders (Saller and Salama 1993; Richelson and Souder 2000).

The active metabolite of quetiapine, N-desalkyl quetiapine, has a high affinity for the histamine H₁ receptor and moderate affinities for the norepinephrine reuptake transporter (NET), the serotonin 5-HT_{1A}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT₇ receptors, the α_{1B} -adrenergic receptor, and the M₁, M₃, and M₅ muscarinic receptors. The compound had low affinities for the 5-HT_{1D}, 5-HT_{2C}, 5-HT₃, 5-HT₅, 5-HT₆, α_{1A} , α_{2A} , α_{2B} , α_{2C} , H₂, M₂, M₄, and dopamine D₁, D₂, D₃, and D₄ receptors.

N-Desalkyl quetiapine potently inhibited human NE transporter about 100-fold more potent than quetiapine itself. N-desalkyl quetiapine was also 10-fold more potent and more efficacious than quetiapine at the 5-HT_{1A} receptor. N-Desalkyl quetiapine was an antagonist at 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, α_{1A} , α_{1D} , α_{2A} , α_{2C} , H₁, M₁, M₃, and M₅ receptors. A moderate affinity for the norepinephrine reuptake inhibitor transporter (NET) and partial 5HT_{1A} agonism, which are considered the possible reason for quetiapine's antidepressant effects as investigated in mouse experiment (Jensen et al 2008). The extent to which the N-desalkyl quetiapine metabolite contributes to the pharmacological activity of quetiapine in humans is not known.

In pre-clinical tests predictive of extrapyramidal symptoms (EPS), quetiapine is unlike standard antipsychotics and has an atypical profile. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. The results of these tests predict that quetiapine should have minimal EPS liability, may also have a lower liability to produce tardive dyskinesia (data on file, AstraZeneca Pharmaceuticals, Wilmington, DE, USA). The production of sustained elevations in prolactin, which is considered a feature of atypical agents, is not evident during quetiapine administration unlike most other antipsychotics (Atmaca et al 2002). However, a study by Alexiadis et al (2002) indicates that oral administration of quetiapine was associated with a marked but transient increase in serum prolactin levels. A recent study investigating the relationship between increased prolactin levels and sexual dysfunction showed that in this 6-week randomized double-blind trial, higher serum prolactin level was related to greater impairment of sexual functioning in male outpatients who were treated with risperidone. This effect was not seen in patient treated with quetiapine (Nakonezny et al 2007).

Pharmacodynamics

Quetiapine and the human plasma metabolite, N-desalkyl quetiapine, interact with a broad range of neurotransmitter receptors. Quetiapine, like clozapine, is an effective antipsychotic at lower D₂ receptor occupancy which may account for its very low risk of EPS and prolactin elevation (Kapur et al 2000; Tauscher-Wisniewski et al 2002). Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin (5HT₂) and dopamine D₁ and D₂ receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂ receptors which is believed

to contribute to the clinical antipsychotic properties and low EPS liability of quetiapine (data on file, AstraZeneca Pharmaceuticals, Wilmington, DE, USA).

Pharmacokinetics: absorption, metabolism, distribution, elimination

Following oral administration quetiapine is extensively metabolized by the liver. Steady state peak molar concentrations of the active metabolite N-desalkyl quetiapine are 35% of that observed for quetiapine. The pharmacokinetics of quetiapine and N-desalkyl quetiapine are linear across the approved dosage range.

At daily doses of 450 to 600 mg the D₂ occupancy of quetiapine fumarate peaks within 2 to 3 hours of its administration (45%–60%) and quickly declines to less than 30% by 12 hours after the last oral dose (Gefvert et al 1998; Kapur et al 2000). Its rapid pharmacokinetics properties necessitate twice-daily dosing, which could lower adherence to the treatment (Iskedjian et al 2002; Diaz et al 2004). However, quetiapine immediate release is clinically also used at once-daily doses. The extended release formulation (XR) of quetiapine fumarate was developed with the goal of achieving similar efficacy and using a once-daily dosing regimen (Kahn et al 2007; Moller et al 2008). Compared to the immediate-release (IR) formulation (DeVane and Nemeroff 2001), the XR formulation shows a more gradual rise in plasma level ($t_{max} = 6$ hours) and a slower decline over a 24-hour period ($t_{1/2} = 7$ hours (data on file, AstraZeneca Pharmaceuticals, Wilmington, DE, USA).

Dose-proportional pharmacokinetics is displayed for doses of quetiapine XR of up to 800 mg administered once daily. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for quetiapine XR when administered once daily are comparable to those achieved for the same total daily dose of immediate-release quetiapine fumarate administered twice daily.

Quetiapine is extensively metabolized by the liver and is approximately 83% bound to plasma proteins. In vitro investigations established that CYP3A4 is likely to be the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. N-desalkyl quetiapine is primarily formed and eliminated via CYP3A4. CYP2D6 and CYP2C9 are also involved in quetiapine metabolism.

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) are weak to modest inhibitors of human cytochrome P450 3A4, 2C19, 2D6, 1A2 and 2C9 activities in vitro. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes.

In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine are approximately 7 and 12 hours respectively (data on file, AstraZeneca Pharmaceuticals, Wilmington, DE, USA).

Efficacy studies of quetiapine XR in MDD and GAD

Efficacy of quetiapine XR in MDD

The efficacy results of quetiapine XR in MDD are presented in Table 1. The six completed double-blind, randomized, placebo-controlled trials with quetiapine XR in MDD can be grouped into 1) monotherapy studies, 2) adjunct studies and 3) maintenance studies.

Monotherapy studies of quetiapine XR in MDD

In a 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study evaluating the efficacy of Quetiapine XR (50, 150, and 300 mg/day) as monotherapy in the treatment of patients with MDD, the primary endpoint was improvement on the Montgomery-Asberg Depression Rating Scale (MADRS) between randomization and week 6 (Weisler et al 2008a). A total of 723 adult patients were randomized: 182, 178, 179, and 184 to quetiapine XR 50, 150, 300 mg/day, and placebo, respectively. Mean scores at baseline were: MADRS 30.9, 30.9, 30.6, and 30.5; Hamilton Depression rating scale (HAM-D) 25.6, 25.5, 25.7, and 25.5; HAM-A 19.6, 19.4, 19.7, and 19.3, respectively. At week 6, all quetiapine XR groups significantly reduced mean MADRS score vs placebo (−11.07): −13.56 ($p \leq 0.05$) for 50 mg, −14.50 ($p \leq 0.001$) for 150 mg, −14.18 ($p \leq 0.01$) for 300 mg.

In a second trial, this time a 10-week, double-blind, randomized, parallel-group, placebo-controlled study, the authors assessed the efficacy of quetiapine XR (150/300 mg/day) as monotherapy for the treatment of MDD using a fixed-dose regime (El-Khalili et al 2008a). A total of 310 patients were randomized to double-blind treatment: 154 quetiapine XR, 156 placebo. The primary endpoint was change from randomization to week 8 in MADRS total score. At week 8, quetiapine XR significantly reduced mean MADRS score vs placebo (−16.49 vs −13.10; $p \leq 0.01$). MADRS response rates were significantly greater at week 8 for quetiapine XR vs placebo (61.9% vs 48.0%; $p \leq 0.05$).

In a third trial using a similar study design (8-week study, multicenter, double-blind, randomized, parallel-group, placebo-controlled) Montgomery et al (2008) investigated

the efficacy of quetiapine XR (150 and 300 mg/day) as monotherapy in the treatment of MDD utilizing an active control group of duloxetine 60 mg/day (Montgomery et al 2008). In this study, 612 adult patients were randomized to receive quetiapine XR 150 mg/day ($n = 152$), quetiapine 300 mg/day ($n = 152$), duloxetine 60 mg/day ($n = 151$) and placebo ($n = 157$). The primary endpoint was change in MADRS total score baseline at week 6. Secondary variables included baseline to week 6 change in HAM-D total scores and Item 1 (depressed mood) scores. Mean MADRS total score (overall baseline mean, 30.15) was significantly reduced at week 6 the quetiapine XR 150 mg/day, quetiapine 300 mg/day and the duloxetine groups compared to the placebo group (−14.81, −15.29, −14.64, −11.18, respectively; $p \leq 0.001$). At week 6, mean HAM-D total scores (overall baseline mean, 25.25) were significantly reduced vs placebo (−10.26) in the quetiapine XR 150 mg/day and 300 mg/day groups (−13.12, −14.02, respectively, $p \leq 0.001$) and duloxetine (−12.37, $p \leq 0.05$). Mean HAM-D Item 1 scores (overall baseline mean, 3.03) were significantly reduced vs placebo (−1.07) by quetiapine XR 150 mg/day, 300 mg/day (−1.49, −1.56, respectively, $p \leq 0.001$) and duloxetine (−1.53, $p \leq 0.001$). Both MADRS response and remission rates were significantly higher in quetiapine XR 300 mg/day and duloxetine as compared to placebo (Table 1). Quetiapine XR 150 mg/day showed robust effects on remission rates in the study by Montgomery et al (2008).

Maintenance treatment in MDD with quetiapine XR monotherapy

The efficacy of quetiapine XR (50–300 mg/day) monotherapy was investigated in a maintenance treatment of patients with MDD in a 52-week, multicenter, double-blind, randomized-withdrawal, parallel-group, placebo-controlled study following an open-label stabilisation period (Datto et al 2008). Primary endpoint was the efficacy of quetiapine XR vs placebo in increasing time from randomization to depressed event as assessed by predefined criteria. A total of 787 patients were randomized to double-blind treatment: 391 quetiapine XR; 385 placebo. The risk of a depressed event was significantly reduced for quetiapine XR vs placebo (implying increased time to the event): HR = 0.34 (0.25, 0.46); $p < 0.0001$. Over the study period, a total of 55 (14.2%) quetiapine XR-treated and 132 (34.4%) placebo-treated patients experienced a depressed event.

Adjunctive treatment with quetiapine XR

Two randomized placebo controlled studies are reported, which examined the adjuvant effects of quetiapine.

Table 1 Studies of quetiapine XR in major depressive disorder (MDD)

Study	Design	N	Comparator	Quetiapine dose	Primary efficacy measure and result	Remission and response rate (%)
Weisler et al 2008a	6-wk, double-blind, randomized, parallel-group, placebo-controlled	723	None	Quetiapine XR (50, 150, 300 mg/day, monotherapy)	Decrease in MADRS score from baseline at 6 wk 50 mg/day: -13.56* 150 mg/day: -14.5*** 300 mg/day: -14.18** Placebo: -11.07	Response ^a 50 mg/day: 42.7** 150 mg/day: 51.2*** 300 mg/day: 44.9** Placebo: 30.3 Remission ^b 50 mg/day: 25.8** 150 mg/day: 20.8*** 300 mg/day: 26.1** Placebo: 18.5
Montgomery et al 2008	8-wk, double-blind, randomized, parallel-group, placebo-controlled, active controlled	612	Duloxetine 60 mg/day	Quetiapine XR 150, 300 mg/day	Decrease in MADRS score baseline to week 6 150 mg/day: -14.8*** 300 mg/day: -15.29*** Duloxetine: -14.64*** Placebo: -11.18	Response ^a Q-XR 150 mg/day: 54.2** Q-XR 300 mg/day: 55.0** Duloxetine: 50.0* Placebo: 37.0 Remission ^b Q-XR 150 mg/day: 26.0 ^{ns} Q-XR 300 mg/day: 31.3* Duloxetine: 31.0* Placebo: 20.0
El-Khalili et al 2008a	10-wk, double-blind, randomized, parallel-group, placebo-controlled	310	none	Quetiapine XR (flexible dose: 150 mg/day; if failure to achieve ≥20% improvement on MADRS, then increase of Q-XR to 300 mg/day, monotherapy)	Decrease in MADRS score from baseline at 8 wk Q-XR 150/300 mg/day: -16.49** Placebo: -13.10	Response ^a Q-XR 150/300 mg/day: 61.9 Placebo: 48.0 Remission ^b Q-XR 150/300 mg/day: 34.7*
Datto et al 2008	52-wk, double-blind, randomized-withdrawal, parallel-group, placebo-controlled	787	none	Quetiapine XR 50–300 mg/day maintenance monotherapy following open-label stabilization period	% of depressive event after 52 wk: Q-XR: 14.2*** Placebo: 34.4 Change in mean MADRS total score during maintenance treatment Q-XR: 0.15*** Placebo: 2.03	none

(Continued)

Table 1 (Continued)

Study	Design	N	Comparator	Quetiapine dose	Primary efficacy measure and result	Remission and response rate (%)
El-Khalili et al 2008b	8-wk, double-blind, randomized, parallel-group, placebo-controlled	446	SSRI/SNRI/TCA/ bupropion	Quetiapine XR 150, 300 mg/day plus AD	Decrease in MADRS score from baseline at 6 wk Q-XR 150 mg/day + AD: -13.6 ^{n.s.} ; Q-XR 300mg/day + AD: -14.7 ^{**} Placebo + AD: -11.7	Response ^a Q-XR 150 mg/day + AD: 52.8 ^{n.s.} ; Q-XR 300 mg/day + AD: 58.9 [*] Placebo + AD: 48.0 Remission ^b Q-XR 150 mg/day + AD: 32.5 ^{n.s.} ; Q-XR 300 mg/day + AD: 42.5 ^{**} Placebo + AD: 24.5
Bauer et al 2008	6-wk, double-blind, randomized, parallel-group, placebo-controlled	787	Maintained previous AD treatment	Quetiapine XR 150, 300 mg/day plus AD	Decrease in MADRS score from baseline at 6 wk Q-XR 150mg/day + AD: -15.26 ^{**} Q-XR 300 mg/day + AD: -14.94 ^{**} Placebo + AD: -12.21	Response ^a Q-XR 150 mg/day + AD: 55.4 ^{n.s.} ; Q-XR 300 mg/day + AD: 57.8 [*] Placebo + AD: 46.3 Remission ^b Q-XR 150 mg/day + AD: 36.1 [*] Q-XR 300 mg/day + AD: 31.1 ^{n.s.} Placebo + AD: 23.8

Q-XR, quetiapine extended release; AD, antidepressant; *p < 0.05; **p < 0.01; ***p < 0.001; ^{n.s.} vs placebo; ^aResponse defined as ≥50% reduction in MADRS total score from baseline; ^bRemission defined as MADRS total score ≤8.

In an 8-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled study the efficacy of Quetiapine XR (150 and 300 mg/day) in combination with an antidepressant for the treatment of MDD and an inadequate response to previous antidepressant treatment was evaluated (El-Khalili et al 2008b). Patients received and antidepressant (SSRI/SNRI/TCA/bupropion) and either quetiapine XR 150 mg/day, 300 mg/day or placebo. The primary endpoint in this study was total change in MADRS score between randomization and week 6. A total of 446 patients were randomized: 148, 150, and 148 to quetiapine XR 150 mg/day, 300 mg/day and placebo, respectively. Mean baseline scores were: MADRS: 27.2, 27.6, and 27.6; HAM-D 24.0, 24.0, and 24.2, respectively. Quetiapine XR 300 mg/day + AD showed significant advantage vs placebo + AD for: 1) change in MADRS total score at week 6 (−14.70 vs −11.7; $p \leq 0.01$); 2) improvement in MADRS from week 1 onwards; 3) response (58.9% vs 46.2%; $p \leq 0.05$); 4) remission (42.5% vs 24.5%; $p \leq 0.01$). For quetiapine XR 150 mg/day + AD improvements in these variables were not significantly different vs placebo.

The second adjunct study using a 6-week, double-blind, randomized, parallel-group, placebo-controlled study design evaluated the efficacy of quetiapine XR (150/300 mg/day) in combination with an antidepressant in the treatment of MDD in patients with an inadequate response to an antidepressant monotherapy. Previous antidepressant treatment was maintained. The primary endpoint was the change in MADRS total score between baseline and week 6. As a result, mean change in MADRS total score (overall baseline mean, 28.4) from baseline to week 6 was significant ($p \leq 0.01$) for quetiapine XR 150 mg/day (−15.26) and 300 mg/day (−14.94) vs placebo (−12.21). Results on response and remission were inconclusive (see Table 1).

Efficacy of quetiapine XR in GAD

The efficacy results of quetiapine XR in GAD are presented in Table 2. While the three controlled published studies investigate quetiapine XR monotherapy in GAD, one of the controlled studies used an active control group of paroxetine.

Monotherapy studies of short-term and long-term treatment with quetiapine XR in GAD

The first study is a 10-week, randomized, double-blind, parallel-group, placebo-controlled trial evaluating the efficacy of quetiapine XR (50, 150, and 300 mg/day) compared with placebo in the treatment of GAD (Khan et al 2008).

The primary endpoint was total score change on the Hamilton Anxiety rating scale (HAM-A) from baseline to week 8. Secondary endpoints included: HAM-A total score change from baseline to Week 1; HAM-A response and remission rates at week 8. A total of 951 patients were randomized: quetiapine XR 50 mg/day ($n = 234$); 150 mg/day ($n = 241$); 300 mg/day ($n = 241$) or placebo ($n = 235$). HAM-A total score mean change from baseline (overall baseline mean 24.6) to week 8 was significantly greater for 50 mg/day (−13.3, $p \leq 0.001$) and 150 mg/day (−13.5, $p \leq 0.001$) but not 300 mg/day (−11.9, $p = 0.24$) vs placebo (−11.1). HAM-A response rates (week 8) were significantly higher for 50 mg/day (60.3%, $p \leq 0.05$) and 150 mg/day (61.5%, $p \leq 0.05$) but not 300 mg/day (54.9%, $p = 0.37$) vs placebo (50.7%). HAM-A remission rates (week 8) were significantly higher for 150 mg/day vs placebo (37.2% vs 27.6%, $p \leq 0.05$); 50 mg/day and 300 mg/day remission rates were 36.1% ($p = 0.08$) and 28.6% ($p = 0.96$), respectively.

In a second study, the long-term efficacy of quetiapine XR monotherapy following an open-label 1 period (50–300 mg/day) in GAD was evaluated in a 52-week, double-blind, randomized-withdrawal, parallel-group, placebo-controlled clinical trial (Katzman et al 2008). Participants received quetiapine XR 4–8-week open-label followed by 12- to 18-week stabilization. Eligible patients (HAM-A ≤ 12 ; MADRS ≤ 16 ; CGI-S ≤ 3) were randomized to quetiapine XR or placebo at last open-label visit dose, which subsequently could be adjusted to 50, 150, or 300 mg/day as clinically indicated. The primary objective was to evaluate the efficacy of quetiapine XR vs placebo in increasing time from randomization to an anxiety event according to predefined criteria. Of the 433 patients who were randomized to double-blind treatment, half received quetiapine XR (216) and placebo (217). The risk of an event was significantly reduced for quetiapine XR vs placebo (implying increased time to the event): HR = 0.19 (0.12, 0.31); $p \leq 0.0001$. Twenty-two quetiapine XR patients experienced an anxiety event which was a significantly lower percentage than the 84 placebo-treated patients who experienced an anxiety event (10.2% vs 38.9%, $p \leq 0.001$). The study concluded that quetiapine XR monotherapy significantly reduced risk of relapse of anxiety events in patients with GAD.

Adjunctive treatment with quetiapine XR

This controlled trial was a 10-week, randomized, double-blind, parallel-group, placebo-controlled, active-controlled study evaluating the efficacy of quetiapine XR (50 and 150 mg/day) compared with placebo for the treatment

Table 2 Studies of quetiapine XR in general anxiety disorder (GAD)

Study	Design	N	Antidepressant	Quetiapine dose	Primary efficacy measure and result	Remission and response rate (%)
Khan et al 2008	10-wk, double-blind, randomized, parallel-group, placebo-controlled	951	none	Quetiapine XR (50, 150, 300 mg/day, monotherapy)	Decrease in HAM-A score from baseline at 8 wk 50 mg/day: -13.31 ^{***} 150 mg/day: -13.54 ^{***} 300 mg/day: -11.87 ^{n.s.} Placebo: -11.07	Response ^a 50 mg/day: 60.3* 150 mg/day: 61.5* 300 mg/day: 54.9 ^{n.s.} Placebo: 50.7 Remission ^b 50 mg/day: 36.1 ^{n.s.} 150 mg/day: 37.2* 300 mg/day: 28.6 ^{n.s.} Placebo: 27.6
Chouinard et al 2008	10-wk, double-blind, randomized, parallel-group, placebo-controlled, active-controlled	873	Paroxetine 20 mg/day	Quetiapine XR (50, 150 mg/day)	Decrease in HAM-A score from baseline at 8 wk 50 mg/day: -13.95* 150 mg/day: -15.96 ^{***} Paroxetine: -14.45** Placebo: -12.30	Response ^a 50 mg/day: 62.6* 150 mg/day: 70.8 ^{***} Paroxetine: 65.9 ^{***} Placebo: 52.1 Remission ^b 50 mg/day: 32.4 ^{n.s.} 150 mg/day: 42.6 ^{***} Paroxetine: 38.8* Placebo: 27.6
Katzman et al 2008a	52-wk, double-blind, randomized-withdrawal, parallel-group, placebo-controlled	433	none	Quetiapine XR 50–300 mg/day maintenance monotherapy following open-label stabilization period	% of anxiety event after 52 wk: Q-XR: 10.2 ^{***} Placebo: 38.9 Change in mean HAM-A total score during maintenance treatment Q-XR: -0.14 ^{***} Q-XR: -0.14 ^{***} Placebo: 1.90	none

Q-XR, quetiapine extended release; AD, antidepressant; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; ^{n.s.} vs placebo; ^aResponse defined as $\geq 50\%$ reduction in HAM-A total score from baseline; ^bRemission defined as HAM-A total score ≤ 7 .

of GAD (Chouinard et al 2008). This study included an active control group of paroxetine 20 mg/day. The primary endpoint employed in this study was the HAM-A total score change from baseline to week 8 and the secondary endpoint considered response and remission criteria. In total, 873 patients were randomized to quetiapine XR 50 mg/day ($n = 221$), 150 mg/day ($n = 218$), paroxetine 20 mg/day ($n = 217$), or placebo ($n = 217$). Mean HAM-A total score (baseline mean, 26.98) was significantly decreased at day 4 by both quetiapine XR doses ($p \leq 0.05$) and at week 8 by quetiapine XR 50 mg/day (-13.95 , $p \leq 0.05$), 150 mg/day (-15.96 , $p \leq 0.001$), and paroxetine (-14.45 , $p \leq 0.01$) vs placebo (-12.30). Quetiapine XR at both doses as well as paroxetine showed significantly higher response and remission rates (except quetiapine XR 50 mg for remission rates) as presented in Table 2.

Safety, tolerability, and adherence in treatment with quetiapine

It has been demonstrated that quetiapine monotherapy is well tolerated for the treatment of bipolar depression (BOLDER study) (Calabrese et al 2005). In this particular study, extra-pyramidal symptoms were assessed with the Simpson-Angus Rating Scale (Simpson and Angus 1970), and akathisia was assessed with the Barnes Rating Scale for Drug-Induced Akathisia (Barnes 1989). The most common side effects of quetiapine included dry mouth, sedation, somnolence, dizziness, and constipation. The most common side effects leading to withdrawal from the study were sedation and somnolence, with most discontinuations occurring within the first week. The most common reasons for withdrawal were related to adverse events in the quetiapine groups (300/600 mg/day) (26.1% and 16.0%) and lack of efficacy in the placebo group (13.3%) (Calabrese et al 2005).

Of importance, changes in weight observed were relatively small and did not result in withdrawal from the study (Calabrese et al 2005). More specifically, during the quetiapine monotherapy study performed by Weisler et al patients in the quetiapine XR 50 ($n = 178$), 150 ($n = 168$), and 300 mg/day ($n = 176$) groups experienced a mean weight change of +0.6 kg, +0.9 kg, and 1.0 kg, respectively, while patients in the placebo group ($n = 178$) experienced a mean weight change of +0.6 kg. The proportion of patients experiencing $\geq 7\%$ increase in weight was 0.6%, 3.6%, 4.5%, and 1.1% for 50, 150, 300 mg/day quetiapine XR, and placebo, respectively (Weisler et al 2008a).

Quetiapine treatment was not associated with treatment-emergent mania. Furthermore, adverse events considered

extra-pyramidal symptoms were present in 8.9% of the 600 mg/day group, 6.7% of the 300 mg/day group, and 2.2% of the placebo group; discontinuation rates for extra-pyramidal symptoms were 2.8%, 1.1%, and 0.6%, respectively.

The side effect profile of quetiapine was assessed in detail in studies by Datto et al (2008) and Montgomery et al (2008) assessing the efficacy of quetiapine XR on MDD. While Table 3 shows that quetiapine XR was more frequently related to dry mouth, sedation, and somnolence than duloxetine and placebo in an 8-week trial, results on adverse events presented in Table 4 indicate that those typical side effects are similar in pattern but slightly less common in long-term treatment of up to 52 weeks with quetiapine. Interestingly, the adverse events reported do not indicate a dose-response relationship for quetiapine XR 150 mg and 300 mg. In all of the above reported studies evaluating the efficacy of quetiapine XR in MDD and GAD no changes on ECG parameters between treatment and placebo were reported.

Impact of quetiapine XR on quality of life

Health-related quality of life measures obtained in randomized-controlled trials are reported for some of the GAD studies. In the studies by Chouinard and by Katzmann quality of life was measured using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). After adjustment for multiplicity (quetiapine groups only), significant increases in Q-LES-Q percent maximum possible total score were seen with quetiapine XR 150 mg and paroxetine compared with placebo at week 8 (13.19, 10.85, and 7.44, respectively) (Chouinard et al 2008) (Figure 1). Similarly, in the study by Katzmann et al (in press) health-related quality of life enjoyment and satisfaction was better with quetiapine XR compared with the placebo group.

Conclusions

While quetiapine has demonstrated efficacy in schizophrenia and bipolar disorder as well as in the treatment of specific symptoms clusters such as agitation and sleep problems in mood disorders, most recent randomized controlled studies show efficacy, safety and tolerability of quetiapine in major depressive disorder and general anxiety disorder, as evaluated in this review. The efficacious application of quetiapine in MDD and GAD ranges from quetiapine monotherapy to adjunctive therapy with antidepressants for short-term and maintenance treatment at a dose range between 50–300 mg/day. The dual action of quetiapine and its active metabolite N-desalkyl quetiapine on the norepinephrine

Table 3 Most common adverse events (AEs) (>5% in any group) during the active treatment period (safety population)

AE, n (%)	Placebo (n = 157)	Quetiapine XR 150 mg/day (n = 152)	Quetiapine XR 300 mg/day (n = 152)	Duloxetine (n = 179)
Dry mouth	14 (8.9)	51 (33.6)	58 (38.2)	28 (18.8)
Sedation	8 (5.1)	59 (38.8)	56 (36.8)	24 (16.1)
Somnolence	11 (7.0)	37 (24.3)	41 (27.0)	19 (12.8)
Dizziness	17 (10.8)	22 (14.5)	29 (19.1)	25 (16.8)
Headache	16 (10.2)	16 (10.5)	14 (9.2)	27 (18.1)
Constipation	10 (6.4)	9 (5.9)	13 (8.6)	17 (11.4)
Irritability	7 (4.5)	2 (1.3)	9 (5.9)	0
Dyspepsia	5 (3.2)	6 (3.9)	8 (5.3)	8 (5.4)
Fatigue	0	4 (2.6)	8 (5.3)	10 (6.7)
Nausea	15 (9.6)	16 (10.5)	8 (5.3)	54 (36.2)
Vision blurred	3 (1.9)	8 (5.3)	8 (5.3)	4 (2.7)
Increased appetite	3 (1.9)	9 (5.9)	6 (3.9)	3 (2.0)
Diarrhea	10 (6.4)	7 (4.6)	4 (2.6)	16 (10.7)
Upper respiratory tract infection	11 (7.0)	3 (2.0)	4 (2.6)	6 (4.0)
Abnormal dreams	1 (0.6)	10 (6.6)	3 (2.0)	4 (2.7)
Pollakiuria	2 (1.3)	5 (3.3)	3 (2.0)	8 (5.4)
Insomnia	11 (7.0)	2 (1.3)	2 (1.3)	22 (14.8)
Decreased appetite	1 (0.6)	5 (3.3)	0	8 (5.4)
Hyperhidrosis	1 (0.6)	0	0	11 (7.4)

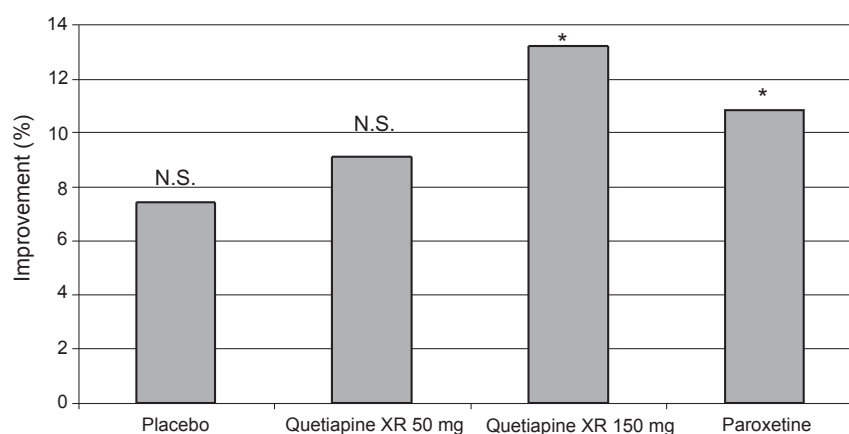
reuptake inhibitor transporter (NET) and the 5HT_{1A} receptor is considered the possible reason for quetiapine's antidepressant effects.

Quetiapine appears to have a specific but overall mild side-effect profile. Some adverse effects such as sedation and somnolence may however lead to withdrawal from treatment

in some patients. Despite the often beneficial sedative effects of quetiapine on clinically relevant sleep problems in psychiatric patients, quetiapine is not recommended solely as a sleeping agent. Overall, the most recently available evidence on quetiapine suggests that it can play a significant role in the management of MDD and GAD.

Table 4 Most common adverse events (AEs) (>5%) occurring in any group during the open-label and randomization treatment phases (safety population)

Preferred term, n (%)	Open-label phase	Randomized phase	
	Quetiapine XR (n = 1078)	Placebo (n = 385)	Quetiapine XR (n = 391)
Dry mouth	259 (24.0)	6 (1.6)	14 (3.6)
Somnolence	362 (33.6)	0	15 (3.8)
Sedation	218 (20.2)	1 (0.3)	10 (2.6)
Dizziness	142 (13.2)	17 (4.4)	26 (6.6)
Fatigue	152 (14.1)	10 (2.6)	17 (4.3)
Weight increased	68 (6.3)	6 (1.6)	38 (9.7)
Headache	93 (8.6)	44 (11.4)	27 (6.9)
Constipation	70 (6.5)	1 (0.3)	8 (2.0)
Nausea	62 (5.8)	38 (9.9)	14 (3.6)
Irritability	93 (8.6)	12 (3.1)	3 (0.8)
Nasopharyngitis	23 (2.1)	25 (6.5)	28 (7.2)
Insomnia	37 (3.4)	57 (14.8)	22 (5.6)
Diarrhea	24 (2.2)	26 (6.8)	21 (5.4)



*P ≤ 0.05 vs placebo; N.S. = not significant from placebo

Figure 1 Improvement of quality of life measures in patients with generalized anxiety disorder.

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