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Review article

Quetiapine XR: Current status for the treatment of major depressive disorder

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ABSTRACT

Quetiapine fumarate extended release (XR) has been approved for treatment of schizophrenia and bipolar disorder. Quetiapine may have antidepressant effects through effects on 5-HT_{2A} receptor, 5-HT_{1A} receptor, dopamine receptor, glutamate receptor and norepinephrine transporter. Recently, 7 large-scale randomized, double-blind, placebo (2-studies with active comparator)-controlled clinical trials have demonstrated that quetiapine XR has clinically meaningful efficacy as monotherapy and adjunct therapy to antidepressants for the treatment of adult patients with major depressive disorder (MDD). In such clinical trials, quetiapine XR was generally well tolerated, although weight gain and changes in metabolic parameters, consistent with the known profile of quetiapine, were observed in some patients. As of December 2009, the United States Food and Drug Administration has approved quetiapine XR for the adjunct treatment of MDD. From the data of currently available clinical trials, this review provides an overview of the data and clinical implications for quetiapine XR in the treatment of MDD to enhance clinicians understanding of the use of quetiapine XR in the treatment of MDD.

Contents

Abbreviations: Adverse event, AE; Extrapyramidal symptoms, EPS; Major depressive disorder, MDD; Extended release, XR; Double-blind, placebo (active comparator)-controlled clinical trials, RCTs; United States Food and drug Administration, US FDA.

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1. Introduction

Most currently marketed antidepressants target either or both the serotonin and norepinephrine systems of the central nervous system to ameliorate depressive symptoms (Stahl, 1998). However, only 40% of patients with major depressive disorder (MDD) achieve remission with initial treatment and show lower response and remission rates if further treatment is needed (Rush et al., 2006). Remission is the ultimate goal of antidepressant treatment, therefore inciting a need for alternative treatment strategies. In this regard, the potential role of atypical antipsychotics such as quetiapine in the treatment of MDD, either as monotherapy or as augmentation therapy has been explored based on preliminary studies in patients with MDD (Endicott et al., 2008; Fleurence et al., 2009; Olver et al., 2008). Aripiprazole has recently been approved as an augmentation therapy by the United States Food and Drug Administration (FDA) for the treatment of MDD.

Atypical antipsychotics were initially introduced for treatment of schizophrenia and related psychotic disorders. When compared with first-generation antipsychotics, atypical antipsychotics possess a lower liability to precipitate extrapyramidal symptoms (EPS) and possibly tardive dyskinesia (Lieberman, 2006; Lieberman et al., 2005).

In addition to proven efficacy in schizophrenia, several atypical antipsychotics have demonstrated efficacy in the treatment of mood disorders (Cruz et al., 2009; Gao et al., 2008; Perlis, 2007). For example, several recently published evidence-based guidelines recommend atypical antipsychotics for the treatment of acute mania and as antidepressant augmentation for treatment-resistant MDD (Baune et al., 2007; Kennedy et al., 2001; Suppes et al., 2005). Moreover, the FDA has approved quetiapine monotherapy for the acute treatment of depressive episodes associated with bipolar disorder and as maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex (U.S. Food and Drug Administration).

Several factors have provided the impetus for this review. Marketing surveillance data indicate that quetiapine and other atypical antipsychotics are prescribed more frequently for depression, anxiety, and sleep syndromes than for primary psychotic disorders (Baune et al., 2007). Taken together, clinicians may portend further usage of atypical antipsychotics for the treatment of mood symptoms, in particular for depressive symptoms.

Quetiapine is an atypical antipsychotic agent widely used as a first-line drug for the treatment of schizophrenia. Atypical agents are characterized by the i) reduced incidence of EPS ii) lower propensity to cause tardive dyskinesia with long-term use compared with typical antipsychotics; and iii) are effective for both positive and negative signs and symptoms of schizophrenia.

This paper reviews currently available literature to address data from randomized, placebo-controlled clinical trials and to update the understanding of clinicians for the role of quetiapine fumarate extended release (quetiapine XR) in the treatment of MDD, by which we may practically enhance the pharmacological options for the treatment of patients with MDD needing further treatment.

We identified relevant studies through a PubMed literature search with a combination of the following search terms: quetiapine, placebo, quetiapine extended release, quetiapine XR, depression, pharmacological treatment. The open-label treatment or case reports were excluded in our search. In addition, relevant literature was identified through the references from retrieved articles. The clinical trial reports from the manufacturer were also identified in the company's clinical trial center (AstraZeneca Pharmaceuticals). Then we thoroughly reviewed major findings from the scanned literatures and eventually synthesized them providing a summary, interpretation, and future direction.

2. Rationale for using quetiapine XR for MDD

Quetiapine enhances central serotonergic neurotransmission through its high affinity for serotonergic receptors (i.e., 5-HT_{2A} receptor antagonism). In particular, 5-HT_{1A} receptor modulation (partial agonism) may also be salient to quetiapine's antidepressant efficacy (Figueroa et al., 2009) and the partial agonistic activity at the 5-HT_{1A} receptor has been known to be prominent in the prefrontal cortex (Ichikawa et al., 2002), which results in an increased extracellular dopamine release in the prefrontal cortex (Yatham et al., 2005). The enhancement effect of quetiapine on dopamine neurotransmission is most likely explained by its antagonism of 5-HT_{2A} and partial agonistic activity at 5-HT_{1A} (Ichikawa et al., 2001). The increase of dopamine D_3 receptor mRNA expression is associated with chronic treatment effects of antidepressants and electroconvulsive treatment (Lammers et al., 2000), thereby D_3 receptor modulation of quetiapine may also be a critical mediator of its antidepressant effect (Stephenson et al., 2000). In addition to its affinity for D_2 and $5HT_2$ receptors, norquetiapine (the major active human metabolite of quetiapine) is also a potent inhibitor of the norepinephrine transporter (NET). PET imaging in non-human primates has demonstrated quetiapine and norquetiapine occupancy at D_2, $5HT_{2A}$, and norquetiapine occupancy at the NET at clinically relevant plasma levels (Nyberg et al., 2007). The clinical relevance of these findings has been supported by PET studies demonstrating NET occupancy by norquetiapine in humans. Evidence from pharmacological and PET studies therefore indicates that moderate D_2 affinity and low-potency D_2 antagonism, combined with high-affinity NET inhibition and 5-HT_{2A} antagonism, may be key characteristics that contribute to the antipsychotic and antidepressant properties of quetiapine (Jensen et al., 2008).

Animal studies have found that quetiapine administration was associated with enhancing the extracellular concentration of noradrenaline as well as dopamine in the rat cerebral cortex (Pira et al., 2004; Tarazi et al., 2000). It is hypothesized that this effect is due to the high affinity of quetiapine for the α_2-adrenergic receptor (Pira et al., 2004). Emerging evidence indicates that its principal active, human plasma metabolite, norquetiapine has a high affinity for, and is a potent inhibitor of, the noradrenaline transporter (NET, $K_i = 35$ nM).

Another hypothesis is that quetiapine is supposed to alter glutamate receptor activity and thus restore normal glutamatergic neurotransmission and reduce the chances of excitotoxicity (Tascedda et al., 1999).

The involvement of quetiapine with inflammatory cytokines (Altschuler and Kast, 2005; Licinio and Wong, 1999; Schiepers et al., 2005), cytoprotection molecules (Rush et al., 1996), or antioxidation process (Xu et al., 2008) may also contribute to improvement of depressive symptoms since they are considered to be associated with the development of depressive symptoms (Miller et al., 2009; Musselman et al., 2003).

Quetiapine treatment is also associated with a decrease in plasma adrenocorticotropic hormone concentration and normalization of HPA-axis dynamics (de Borja Goncalves Guerra et al., 2005).

3. Clinical trial data for use of quetiapine in MDD

There have been 7 quetiapine XR clinical trials for the treatment of adult patients with MDD. These trials are all randomized, placebo-

controlled, double-blind studies (RCTs) with quetiapine XR either as an adjunct therapy or as monotherapy [except for open-label extension study (AstraZeneca Pharmaceuticals D1448C00005)], of which four studies have been published (Bauer et al., 2009; Cutler et al., 2009; El-Khalali et al., 2010; Weisler et al., 2009) The other studies remain as data on file of the manufacturer (AstraZeneca Pharmaceuticals D1448C00003; AstraZeneca Pharmaceuticals I. D1448C00004; AstraZeneca Pharmaceuticals D1448C00005). As for the short-term RCTs(AstraZeneca Pharmaceuticals D1448C00003; AstraZeneca Pharmaceuticals D1448C00004; Bauer et al., 2009; Cutler et al., 2009; El-Khalali et al., 2010; Weisler et al., 2009), 3055 patients were randomized and 1773 (58.0%) completed the study, and 1854 patients participated and 776 were randomized in the 52-week long-term study (AstraZeneca Pharmaceuticals D1448C00005). Table 1 represents patients' disposition and characteristics of the 7 studies.

In these RCTs, the primary outcome measures were the mean changes in total score of Montgomery–Åsberg Depression Rating Scale (MADRS) total score for short-term trials and the time to depression relapse (defined as a depressive event) in the long-term study. Principal secondary assessments included the Hamilton Depression Rating Scale-17 item (HAM-D-17) and the Hamilton Anxiety Rating Scale (HAM-A), Quality of Life Enjoyment Satisfaction-Questionnaire (Q-LES-Q), Clinical Global Impression-Severity of illness (CGI-S), CGI-I, and adverse events (AEs). Response was defined as showing a ≥50% reduction in MADRS total score from baseline to end of treatment and remission was defined as a MADRS total score ≤8 at the end of treatment.

3.1. Primary endpoint

3.1.1. Short-term study

3.1.1.1. Monotherapy studies. In the Weisler et al. (D1448C00001) 8-week, multicenter RCT evaluating the efficacy of quetiapine XR (50, 150, and 300 mg/day) as monotherapy in the treatment of patients with MDD, it was observed that each dose of quetiapine XR significantly reduced the mean MADRS total score compared with placebo, showing a magnitude of treatment difference of 2.5, 3.4, and 3.1, respectively (Weisler et al., 2009). In addition, given the *p*-values, all quetiapine XR-treatment groups separated from placebo in the MADRS total score by Day 4 (*p*-values relative to placebo: 0.006 for quetiapine XR 50 mg/day, <0.001 for quetiapine XR 150 mg/day, and <0.001 for quetiapine XR 300 mg/day). The significant and greater changes in the MADRS total scores for quetiapine XR over placebo were also replicated in the Cutler et al. (D1448C00002) 8 week, monotherapy RCT as well (Cutler et al., 2009). In this study, quetiapine XR 150 mg/day (49.7% decreases than baseline) and 300 mg/day (50.8% decreases than baseline), and duloxetine (48% decreases than baseline) significantly reduced mean MADRS total score versus placebo (37% decreases than baseline). A significant reduction was also seen at Week 1 with quetiapine XR 150 mg/day and 300 mg/day versus placebo, while it was not observed with duloxetine. A further 8-week RCT study of quetiapine XR with flexible dose has also demonstrated superior efficacy over placebo (AstraZeneca Pharmaceuticals D1448C00003). The quetiapine XR-treated group showed significantly greater improvement in the MADRS total scores at week 1 of treatment (the mean difference from placebo in change from randomization was −1.9, $p=0.01$), and such improvements were retained until the end of treatment (magnitude of treatment difference was 3.4 in the mean change in MADRS total scores between the two groups during the study). In the study of D1448C00004, an 8-week, short-term monotherapy study of quetiapine XR including active comparator (escitalopram) (AstraZeneca Pharmaceuticals D1448C00004), contrary to the previous short-term studies, quetiapine XR with flexible dose (50–300 mg/day) failed to separate from placebo in the mean change in MADRS total scores from baseline to end of treatment, although quetiapine XR showed numerically greater improvements over placebo. The active comparator escitalopram also failed to separate from placebo making this a failed study overall. In this study, the separation between quetiapine XR and placebo in the MADRS total score was observed by Week 2 (the mean change from randomization, quetiapine XR vs placebo = −2.3, $p=0.011$) and was maintained until Week 4 (−2.8, $p=0.005$). Separation from placebo was also demonstrated by Week 4 in the escitalopram-treatment group (the mean change from randomization, escitalopram vs placebo = −2.3, $p=0.021$); however, superiority of

Table 1
The patients' disposition in the 7 randomized, placebo-controlled clinical trials of quetiapine XR.

Study ID/design	Drugs	Randomized (*n*)	Safety (*n*)	ITT (*n*)	Discontinuation (*n*)	Completed (*n*) (randomized treatment)	Completed (*n*) (complete treatment period)
D1448C00001 (Weisler et al., 2009)/8-week	PBO	184	181	178	50	134	95
(6-week randomized-phase; 2-week, DTTP),	QTP 50 mg/day	182	181	178	48	134	103
r, db, and fixed-dose monotherapy	QTP 150 mg/day	178	176	168	55	123	89
	QTP 300 mg/day	179	179	176	59	120	85
D1448C00002 (Cutler et al., 2009)/8-week	PBO	157	157	152	33	124	100
(6-week randomized-phase; 2-week DTTP),	DLX 60 mg/day	151	149	141	46	105	71
r, db, ac, and fixed-dose monotherapy	QTP 150 mg/day	152	152	147	52	100	73
	QTP 300 mg/day	152	152	147	39	113	92
D1448C00003 (AstraZeneca Pharmaceuticals)/8-week	PBO	156	155	152	45	111	78
(6-week randomized-phase; 2-week DTTP),	QTP 150–300 mg/day	154	152	147	46	108	81
r, db, and flexible-dose monotherapy							
D1448C00004 (AstraZeneca Pharmaceuticals)/8-week	PBO	157	155	153	40	117	73
(6-week randomized-phase; 2-week,DTTP),	ECTP 10–20 mg/day	157	156	152	39	118	69
r, db, ac, and flexible-dose monotherapy	QTP 50-300 mg/day	157	157	154	50	107	81
D1448C0006 (El-Khalali et al., 2010)/8-week	PBO	148	148	143	23	125	99
(6-week randomized-phase; 2-week drug- DTTP),	QTP 150 mg/day	148	148	143	34	114	92
r, db, and fixed-dose add-on therapy	QTP 300 mg/day	150	149	146	45	105	68
D1448C00007 (Bauer et al., 2009)/6-week,	PBO	163	161	160	18	NA	145
r, db, and fixed-dose add-on therapy	QTP 150 mg/day	167	167	166	21	NA	146
	QTP 300 mg/day	163	163	161	30	NA	133
D1448C00005 (AstraZeneca Pharmaceuticals)/open-label		*N* OL safety	*N* randomized safety	ITT *n*		*N* PP	
(OL) run- in phase for 8 weeks, OL stabilization phase	PBO	NA	385	384		290	
for 12 weeks and r phase for 52 weeks	QTP 50–300 mg/day	1854	391	387		303	

Data represent a number.
Abbreviations: PBO, placebo; QTP, quetiapine; DLX, duloxetine; ECTP, escitalopram; ITT, intent-to-treat; DTTP, drug-discontinuation/tapering phase; r, randomized; db, double-blind; and ac, active comparator.

escitalopram over placebo was not demonstrated at any other timepoint or at the end of treatment.

3.1.1.2. Adjunct therapy studies. Two RCTs (Bauer et al., 2009; El-Khalali et al., 2010) of adjunct quetiapine XR in patients with MDD with an inadequate response to ≥1 antidepressant have been conducted, both of which have been published. In the first adjunct RCT (El-Khalali et al., 2010), quetiapine XR 150 mg/day showed a numerically higher reduction in the MADRS total score compared with placebo, but failed to find a statistical difference, while quetiapine XR 300 mg/day demonstrated a statistically significant superiority to placebo during the study ($p<0.01$). However, the mean change in MADRS total score from baseline in the quetiapine XR 150 mg/day treatment group was superior to placebo at Week 1 (−9.1 vs −6.0, $p<0.001$) as well as seen also in the quetiapine XR 300 mg/day group (−8.20 vs −6.0, $p=0.002$). Although, in the first adjunct quetiapine XR RCT (El-Khalali et al., 2010), quetiapine XR 150 mg/day failed to show an efficacy over placebo, the second adjunct quetiapine XR study clearly demonstrated superior efficacy over placebo (43.3% decrease) at doses of 150 mg/day (53.4% decrease) and 300 mg/day (52.6% decrease) as measured by the mean change in the MADRS total score from baseline to the end of treatment (Bauer et al., 2009). In addition, a separation from placebo in MADRS total score started at Week 1 ($p<0.001$) and was maintained throughout the study period. Table 2 summarizes the efficacy findings of the individual studies.

3.1.2. Long-term study

A 52-week, open-label extension study of quetiapine XR was conducted, in which 1854 patients received quetiapine XR during the 12-week open-label stabilization phase of the study and 776 patients were randomized to receive either quetiapine XR ($n=391$) or placebo ($n=385$) for up to 52 weeks (AstraZeneca Pharmaceuticals D1448C00005). Quetiapine XR was found to be significantly superior to placebo in maintaining improvement of depression symptoms during the study, as demonstrated by the number of subjects who relapsed (132 [34.4%] vs 55 [14.2%], $p<0.001$; hazard ratio = 0.34 [95% confidence interval = 0.25–0.46]).

3.2. Secondary endpoints

3.2.1. Response and remission rates

Response rates (defined as a ≥50% improvement in MADRS total score) from the short-term monotherapy RCTs with flexible-dose quetiapine XR (50–300 mg/day) and two adjunct therapy RCTs (fixed dose of quetiapine XR 150 mg/day) failed to show significant differences compared with placebo. As for remission (defined as a MADRS total score ≤8), the results are more discouraging than the response rates. In monotherapy RCTs, the two flexible-dose RCTs (50–300 mg/day and 150–300 mg/day), one fixed-dose RCT (50, 150, or 300 mg/day) and the other fixed-dose RCT (150 mg/day-treated group but not the 300 mg/day-treated group) failed to demonstrate a superiority over placebo in terms of the proportion of patients who achieved remission. The two-fixed dose, adjunct therapy studies (150 mg/day and 300 mg/day) failed to show superiority over placebo in remission rates; in one study quetiapine XR 150 mg/day failed, while in the other study quetiapine XR 300 mg/day failed. Table 2 shows all the response and remission rates from the 6 short-term studies. Number-needed-to treat (NNT) is also calculated from the studies and presented in Table 2.

3.3. Other secondary endpoints

3.3.1. Monotherapy studies

Overall results from the secondary outcome variables in the short-term monotherapy RCTs have supported the primary endpoint. However, quality of life measure was not changed after treatment with quetiapine XR.

3.4. Adjunct therapy studies

The findings from the secondary outcome variables in the short-term adjunct quetiapine XR RCTs (Bauer et al., 2009; El-Khalali et al., 2010) showed a similar trend toward superiority of quetiapine XR over placebo treatment as seen in primary endpoint analyses.

However, a change in HAM-D-17 and CGI-S total scores gave inconsistent results which may possibly be a result of potential differences in baseline characteristics across the studies or an inadequate sensitivity of such rating scales to detect differences between the drug and placebo. Finally, quetiapine XR failed to show a significantly greater reduction in the Q-LES-Q total score from baseline to end of treatment compared with the placebo-treated group. Aforementioned issues need to be addressed in future studies.

4. Safety and tolerability of quetiapine XR in MDD

It has been shown in clinical trials that quetiapine XR as monotherapy or adjunct therapy was found to be generally well tolerated in the treatment of MDD. Quetiapine XR at doses of 50 mg/day, 150 mg/day, and 300 mg/day were generally well tolerated, and the overall incidence of adverse events (AEs) showed a trend toward higher proportion in the quetiapine XR-treatment groups in a dose-dependent manner. The most common AEs were dry mouth, sedation, headache and somnolence across all the studies. Most AEs were mild to moderate in all treatment groups. Serious AEs (SAEs) were infrequent in all treatment groups.

This favorable safety and tolerability profile of quetiapine XR in patients with MDD was also replicated in the long-term 52-week study (AstraZeneca Pharmaceuticals D1448C00005). The proportion of patients who had reported AEs and overall AE rates reported in the individual study are presented in Tables 3–5.

In the first RCT (Weisler et al., 2009), patients who received quetiapine XR 50 ($n=178$), 150 ($n=168$), and 300 mg/day ($n=176$) 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 ≥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. These small increases in weight were similar across the studies. Overall, weight increase with quetiapine XR was double in comparison with placebo.

The most common AEs potentially related to EPS were akathisia, restlessness, extrapyramidal disorder, and tremor. Overall, the assessment of parkinsonian and akathisia symptoms as assessed by Simpson–Angus Scale total scores and Barnes Akathisia Rating Scale global assessment scores indicated that quetiapine XR treatment was similar to placebo across the studies, and an improvement or no worsening in symptoms was noted in most patients in all active treatment groups at the end of treatment. In addition, these AEs were not higher with quetiapine XR than duloxetine (Cutler et al., 2009) or escitalopram (AstraZeneca Pharmaceuticals D1448C00004) which were used as active comparators.

A small increase in mean pulse rate, confirmed by electrocardiographic measurement of heart rate, was observed in the quetiapine XR groups across the studies, although they were considered clinically meaningless.

The common AEs frequently experienced in the short-term RCTs and open-label phase of the 52-week study were dry mouth, sedation and somnolence, however, these AEs were observed significantly less during the randomized phase of the 52-week study. For instance, only 3.6% (14/391) and 3.8% (15/391) of patients experienced dry mouth and somnolence, respectively. No major differences were observed in mean changes for most laboratory parameters between the quetiapine

Table 2
The response and remission rates defined by a Montgomery–Åsberg Depression Rating Scale (MADRS) total score and number-needed-to treat (NNT) in the 6 short-term randomized, placebo-controlled clinical trials of quetiapine XR.

Study ID/design	Drugs	MADRS change	Response (%)	Remission (%)	NNT (response/remission)
D1448C00001 (Weisler et al., 2009)/8-week	PBO	−11.1	30.3	18.5	
(6-week randomized-phase; 2-week DTTP),	QTP 50 mg/day	−13.6*	42.7**	25.8	8/14
r, db, and fixed dose	QTP 150 mg/day	−14.5**	51.2***	20.8	5/43
	QTP 300 mg/day	−14.2**	44.9***	26.1	7/13
D1448C00002 (Cutler et al., 2009)/8-week	PBO	−11.2	36.2	20.4	
(6-week randomized-phase; 2-week DTTP),	DLX 60 mg/day	−14.6***	49.6*	31.9*	7/9
r, db, ac, and fixed dose	QTP 150 mg/day	−14.8***	54.4**	26.5	5/16
	QTP 300 mg/day	−15.3***	55.1***	32.0*	5/9
D1448C00003 (AstraZeneca Pharaceuticals)/8-week	PBO	−13.1	48.0	25.0	
(6-week randomized-phase; 2-week DTTP),	QTP 150–300 mg/day	−16.5**	61.9*	34.7†	7/10
r, db, and flexible dose					
D1448C00004 (AstraZeneca Pharmaceuticals)/8-week	Total				
(6-week randomized-phase; 2-week DTTP),	PBO	−15.6	51.0	35.3	
r, db, ac, and flexible dose	ECTP 10–20 mg/day	−16.7	59.9	40.8	11/18
	QTP 50–300 mg/day	−17.2	60.4	35.7	11/250
D1448C00006 (El-Khalali et al., 2010)/8-week	PBO	−11.7	46.2	24.5	
(6-week randomized-phase; 2-week DTTP),	QTP 150 mg/day	−13.6	51.7	35.0	18/10
r, db, and fixed dose	QTP 300 mg/day	−14.7**	58.9*	42.5**	8/6
D1448C00007 (Bauer et al., 2009)/6-week,	PBO	−12.2	46.3	23.8	
r, db, and fixed dose	QTP 150 mg/day	−15.3**	55.4	36.1*	11/8
	QTP 300 mg/day	−14.9**	57.8*	31.1	9/14

Data represent a number if not specified. p-values are all versus placebo.
Abbreviations: PBO, placebo; QTP, quetiapine; DLX, duloxetine; ECTP, escitalopram; DTTP, drug-discontinuation/tapering phase r, randomized; db, double-blind; and ac, active comparator.
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.
† $p=0.052$ vs. PBO.

XR and placebo groups. The mean weight increase was +1.9 kg at the end of treatment. Although, increases in glucose and triglycerides level were higher in the quetiapine XR group than in the placebo group, they were in a similar range in comparison with those seen in short-term RCTs.

The most notable changes in clinical chemistry parameters involved glucose and triglyceride. In fact, the mean increase in glucose level was 3.4 mg/dL (150 mg/day) and 4.6 mg/dL (300 mg/day), while 1.6 mg/dL and 1.3 mg/dL for duloxetine and placebo, respectively (Cutler et al., 2009). The mean increases in triglycerides were 10 mg/dL and 17.6 mg/dL for quetiapine XR 150 mg/day and quetiapine XR 300 mg/day, respectively, while 10.2 mg/dL and 3.9 mg/dL for duloxetine and placebo, respectively (Cutler et al., 2009). These findings were similar across the studies. Hence clinicians need to be aware of the potential changes in these metabolic parameters when treating patients with MDD with quetiapine XR.

In summary, based on these findings, the most commonly reported AEs for quetiapine XR in the treatment of MDD were dry mouth, sedation, and somnolence. The most common AEs reported for duloxetine in these studies were nausea, dry mouth and

Table 3
Patients who had an adverse event (AE) in the RCTs of quetiapine XR for treatment of major depressive disorder (MDD).

Study ID/design	Drugs	Safety (*n*)	Any AEs	Drug-related AEs	AEs leading to discontinuation
D1448C00001 (Weisler et al., 2009)	PBO	181	126 (69.6)	86 (47.5)	14 (7.7)
	QTP 50 mg/day	181	144 (79.6)	123 (68.0)	16 (8.8)
	QTP 150 mg/day	176	150 (85.2)	132 (75.0)	26 (14.8)
	QTP 300 mg/day	179	158 (88.3)	141 (78.8)	33 (18.4)
D1448C00002 (Cutler et al., 2009)	PBO	157	114 (72.6)	78 (49.7)	9 (5.7)
	DLX 60 mg/day	149	131 (87.9)	112 (75.2)	27 (18.1)
	QTP 150 mg/day	152	137 (90.1)	124 (81.6)	33 (21.7)
	QTP 300 mg/day	152	139 (91.4)	125 (82.2)	23 (15.1)
D1448C00003 (AstraZeneca Pharmaceuticals D1448C00003)	PBO	155	96 (61.9)	44 (28.4)	4 (2.6)
	QTP 150–300 mg/day	152	125 (82.2)	101 (66.4)	15 (9.9)
D1448C00004 (AstraZeneca Pharmaceuticals I. D1448C00004)	PBO	155	114 (73.5)	81 (52.3)	7 (4.5)
	ECTP 10–20 mg/day	156	127 (81.4)	106 (67.9)	11 (7.1)
	QTP 50–300 mg/day	157	136 (86.6)	125 (79.6)	25 (15.9)
D1448C00006 (El-Khalali et al., 2010)	PBO	148	99 (66.9)	52 (35.1)	0
	QTP 150 mg/day	148	122 (82.4)	105 (70.9)	17 (11.5)
	QTP 300 mg/day	149	130 (87.2)	111 (74.5)	29 (19.5)
D1448C00007 (Bauer et al., 2009)	PBO	161	87 (54.0)	40 (24.8)	6 (3.7)
	QTP 150 v	167	109 (65.3)	83 (49.7)	11 (6.6)
	QTP 300 mg/day	163	122 (74.8)	107 (65.6)	19 (11.7)
D1448C00005 (AstraZeneca Pharmaceuticals D1448C00005)		*N*, randomized safety			
	PBO	385	233 (60.5)	109 (28.3)	20 (5.2)
	QTP 50–300 mg/day	391	246 (62.9)	129 (33.0)	25 (6.4)

Data represent number (%).

Table 4
Adverse events (AEs, > 5% in any treatment groups across studies) in the monotherapy RCTs of quetiapine XR for treatment of major depressive disorder (MDD).

	D1448C00001 (Weisler et al., 2009)				D1448C00002 (Cutler et al., 2009)				D1448C00003 (AstraZeneca Pharmaceuticals D1448C00003)		D1448C00004 (AstraZeneca Pharmaceuticals D1448C00004)		
	PBO	QTP 50	QTP 150	QTP 300	PBO	QTP 150	QTP 300	DLX	PBO	QTP	PBO	QTP	ESC
Dry mouth	16 (8.8)	40 (22.1)	66 (37.5)	74 (41.3)	14 (8.9)	51 (33.6)	59 (38.8)	31 (20.8)	10 (6.5)	51 (33.6)	13 (8.4)	60 (38.2)	22 (14.1)
Sedation	11 (6.1)	49 (27.1)	63 (35.8)	55 (30.7)	9 (5.7)	59 (38.8)	57 (37.5)	24 (16.1)	4 (2.6)	35 (23.0)	5 (3.2)	17 (10.8)	8 (5.1)
Somnolence	20 (11.0)	33 (18.2)	35 (19.9)	52 (29.1)	11 (7.0)	37 (24.3)	42 (27.6)	20 (13.4)	8 (5.2)	31 (20.4)	6 (3.9)	56 (35.7)	13 (8.3)
Headache	27 (14.9)	22 (12.2)	24 (13.6)	26 (14.5)	20 (12.7)	21 (13.8)	19 (12.5)	32 (21.5)	16 (10.3)	22 (14.5)	49 (31.6)	41 (26.1)	49 (31.4)
Dizziness	10 (5.5)	16 (8.8)	19 (10.8)	19 (10.6)	18 (11.5)	24 (15.8)	30 (19.7)	31 (20.8)	6 (3.9)	13 (8.6)	22 (14.2)	53 (33.8)	29 (18.6)
Nausea	11 (6.1)	14 (7.7)	15 (8.5)	16 (8.9)	16 (10.2)	25 (16.4)	14 (9.2)	56 (37.6)	11 (7.1)	10 (6.6)	30 (19.4)	34 (21.7)	47 (30.1)
Insomnia	14 (7.7)	9 (5.0)	12 (6.8)	12 (6.7)	13 (8.3)	11 (7.2)	5 (3.3)	24 (16.1)	4 (2.6)	14 (9.2)	22 (14.2)	22 (14.0)	23 (14.7)
Diarrhea	16 (8.8)	12 (6.6)	11 (6.3)	6 (3.4)	14 (8.9)	11 (7.2)	8 (5.3)	19 (12.8)	6 (3.9)	10 (6.6)	11 (7.1)	19 (12.1)	19 (12.2)
Constipation	5 (2.8)	13 (7.2)	15 (8.5)	16 (8.9)	10 (6.4)	9 (5.9)	14 (9.2)	17 (11.4)	2 (1.3)	9 (5.9)	7 (4.5)	20 (12.7)	13 (8.3)
Nasopharyngitis	5 (2.8)	3 (1.7)	6 (3.4)	2 (1.1)	6 (3.8)	7 (4.6)	7 (4.6)	2 (1.3)	11 (7.1)	4 (2.6)	9 (5.8)	2 (1.3)	7 (4.5)
Increased appetite	7 (3.9)	8 (4.4)	9 (5.1)	8 (4.5)	3 (1.9)	9 (5.9)	6 (3.9)	3 (2.0)	2 (1.3)	10 (6.6)	6 (3.9)	11 (7.0)	3 (1.9)
Irritability	7 (3.9)	11 (6.1)	10 (5.7)	6 (3.4)	7 (4.5)	4 (2.6)	10 (6.6)	2 (1.3)	2 (1.3)	6 (3.9)	8 (5.2)	9 (5.7)	8 (5.1)
Fatigue	8 (4.4)	11 (6.1)	14 (8.0)	11 (6.1)	1 (0.6)	4 (2.6)	10 (6.6)	11 (7.4)	0	11 (7.2)	8 (5.2)	19 (12.1)	14 (9.0)
Dyspepsia	5 (2.8)	4 (2.2)	10 (5.7)	5 (2.8)	5 (3.2)	6 (3.9)	8 (5.3)	8 (5.4)	2 (1.3)	4 (2.6)	9 (5.8)	12 (7.6)	5 (3.2)
Myalgia	3 (1.7)	8 (4.4)	13 (7.4)	4 (2.2)	3 (1.9)	5 (3.3)	5 (3.3)	3 (2.0)	1 (0.6)	3 (2.0)	6 (3.9)	11 (7.0)	12 (7.7)
Vomiting	4 (2.2)	3 (1.7)	4 (2.3)	12 (6.7)	3 (1.9)	10 (6.6)	4 (2.6)	7 (4.7)	4 (2.6)	8 (5.3)	3 (1.9)	9 (5.7)	6 (3.8)
Back pain	4 (2.2)	3 (1.7)	10 (5.7)	9 (5.0)	3 (1.9)	7 (4.6)	6 (3.9)	6 (4.0)	2 (1.3)	3 (2.0)	2 (1.3)	0	3. (1.9)
Hyperhidrosis	2 (1.1)	0	2 (1.1)	2 (1.1)	1 (0.6)	0	1 (0.7)	11 (7.4)	0	1 (0.7)	9 (5.8)	8 (5.1)	12 (7.7)
Vision blurred	2 (1.1)	3 (1.7)	3 (1.7)	8 (4.5)	3 (1.9)	8 (5.3)	8 (5.3)	4 (2.7)	0	5 (3.3)	5 (3.2)	6 (3.8)	4 (2.6)
Abnormal dreams	7 (3.9)	3 (1.7)	4 (2.3)	3 (1.7)	3 (1.9)	10 (6.6)	5 (3.3)	5 (3.4)	1 (0.6)	1 (0.7)	0	0	2 (1.3)
Pollakiuria	4 (2.2)	2 (1.1)	3 (1.7)	0	2 (1.3)	5 (3.3)	3 (2.0)	8 (5.4)	0	2 (1.3)	6 (3.9)	1 (0.6)	0
Tremor	3 (1.7)	5 (2.8)	3 (1.7)	3 (1.7)	2 (1.3)	2 (1.3)	3 (2.0)	8 (5.4)	0	0	2 (1.3)	4 (2.5)	6 (3.8)
Decreased appetite	1 (0.6)	3 (1.7)	3 (1.7)	3 (1.7)	1 (0.6)	5 (3.3)	1 (0.7)	8 (5.4)	0	2 (1.3)	3 (1.9)	4 (2.5)	5 (3.2)
Nasal congestion	2 (1.1)	1 (0.6)	3 (1.7)	3 (1.7)	4 (2.5)	2 (1.3)	7 (4.6)	1 (0.7)	3 (1.9)	9 (5.9)	1 (0.6)	4 (2.5)	0
Arthralgia	5 (2.8)	3 (1.7)	5 (2.8)	5 (2.8)	3 (1.9)	4 (2.6)	4 (2.6)	0	4 (2.6)	9 (5.9)	5 (3.2)	8 (5.1)	1 (0.6)
Influenza	2 (1.1)	3 (1.7)	3 (1.7)	2 (1.1)	2 (1.3)	1 (0.7)	1 (0.7)	3 (2.0)	1 (0.6)	2 (1.3)	4 (2.6)	8 (5.1)	3 (1.9)
Palpitations	4 (2.2)	2 (1.1)	3 (1.7)	1 (0.6)	3 (1.9)	2 (1.3)	6 (3.9)	2 (1.3)	2 (1.3)	0	6 (3.9)	6 (3.8)	8 (5.1)
Anxiety	1 (0.6)	2 (1.1)	2 (1.1)	3 (1.7)	7 (4.5)	4 (2.6)	6 (3.9)	5 (3.4)	3 (1.9)	3 (2.0)	4 (2.6)	12 (7.6)	7 (4.5)
Abdominal pain upper	1 (0.6)	1 (0.6)	0	1 (0.6)	4 (2.5)	1 (0.7)	2 (1.3)	5 (3.4)	0	4 (2.6)	6 (3.9)	9 (5.7)	5 (3.2)
Hypersomnia	0	1 (0.6)	4 (2.3)	1 (0.6)	0	1 (0.7)	2 (1.3)	0	0	0	1 (0.6)	9 (5.7)	2 (1.3)

Data represent number (%).
Abbreviations: PBO, placebo; QTP, quetiapine XR.

headache whilst those reported for escitalopram were headache, nausea and dizziness. Glucose and lipid levels were higher with quetiapine XR than duloxetine, escitalopram, and placebo. However, EPS-related AEs were comparable with active comparators and placebo. Interestingly, currently available findings have suggested that the incidences of AEs were not dose related, for quetiapine XR 150 mg/day and 300 mg/day. These favorable safety and tolerability profile of quetiapine XR may be maintained in long-term treatment as seen in the 52-week study. The pattern of common AEs observed with quetiapine XR generally conformed to that which was anticipated based on the known pharmacological profile of quetiapine XR.

5. Clinical implications for the use of quetiapine XR for MDD

5.1. Faster treatment response onset

Evidence indicates that approximately 50% of antidepressant responders at 8 weeks were found to show a response by Week 2 and over 75% started to respond by Week 4 (Nierenberg et al., 1995).

Table 5
Adverse events (AEs, >5% in any treatment groups across studies) in the adjunct RCTs of quetiapine XR for treatment of major depressive disorder (MDD).

	D1448C00006 (El-Khalali et al., 2010)			Bauer et al., 2009		
	PBO	QTP 150	QTP 300	PBO	QTP 150	QTP 300
Dry mouth	13 (8.8)	52 (35.1)	66 (44.3)	11 (6.8)	34 (20.4)	58 (35.6)
Sedation	6 (4.1)	25 (16.9)	33 (22.1)	7 (4.3)	16 (9.6)	21 (12.9)
Somnolence	6 (4.1)	43 (29.1)	43 (28.9)	5 (3.1)	28 (16.8)	38 (23.3)
Headache	20 (13.5)	21 (14.2)	11 (7.4)	16 (9.9)	15 (9.0)	13 (8.0)
Dizziness	8 (5.4)	17 (11.5)	21 (14.1)	12 (7.5)	19 (11.4)	15 (9.2)
Nausea	12 (8.1)	13 (8.8)	15 (10.1)	10 (6.2)	9 (5.4)	9 (5.5)
Insomnia	10 (6.8)	16 (10.8)	12 (8.1)	7 (4.3)	3 (1.8)	2 (1.2)
Diarrhea	10 (6.8)	10 (6.8)	10 (6.7)	3 (1.9)	1 (0.6)	0
Constipation	5 (3.4)	11 (7.4)	16 (10.7)	6 (3.7)	7 (4.2)	17(10.4)
Nasopharyngitis	2 (1.4)	5 (3.4)	4 (2.7)	10 (6.2)	5 (3.0)	5 (3.1)
Increased appetite	8 (5.4)	8 (5.4)	10 (6.7)	0	1 (0.6)	4 (2.5)
Irritability	9 (6.1)	9 (6.1)	5 (3.4)	0	3 (1.8)	0
Fatigue	7 (4.7)	23 (15.5)	10 (6.7)	5 (3.1)	22 (13.2)	24 (14.7)

Data represent number (%).
Abbreviations: PBO, placebo; and QTP, quetiapine XR.

Meanwhile, delayed onset of antidepressant response is related to poor clinical outcomes resulting in significant poor adherence and subsequent relapse and recurrence. In addition, previously published research (Nierenberg et al., 1995; Papakostas et al., 2007) report similar findings i.e., non-response within the first 2 weeks of treatment predicted poorer 8-week outcomes. In this regard, quetiapine XR monotherapy demonstrated its efficacy as early as Day 4 across the dose range (50 mg/day, 150 mg/day, and 300 mg/day) (Weisler et al., 2009). Other monotherapy RCTs have also replicated the earlier effect of quetiapine XR as early as Week 1 or Week 2 (Cutler et al., 2009). In addition, adjunct quetiapine XR separated from placebo as early as Week 1 (Bauer et al., 2009; El-Khalali et al., 2010). Hence, quetiapine XR as a monotherapy or adjunct therapy may potentially shorten the response time as seen in clinical trials with aripiprazole for treating patients with MDD.

5.2. Drug interaction with antidepressant

Overall, adjunct quetiapine XR in combination with currently marketed antidepressants, regardless of class, seems to require a dose adjustment within the approved antidepressant dose range (in the adjunct quetiapine XR RCTs, the mean doses of all combined antidepressants were in the range of approved dose) but clinicians may need to pay attention to individual patient's response and potential clinical factors relating to tolerability. Considering the pharmacokinetic profile of quetiapine XR, antidepressant inducing or inhibiting effect on CYP450 3A4 should be cautiously combined. However, there are no data to indicate any deviated findings against quetiapine XR in combination with various classes of antidepressants.

5.3. Proper dosing

In the 7 quetiapine XR MDD studies, dosing of quetiapine XR was tested in adult patients at 50, 150 and 300 mg/day in the fixed-dose monotherapy studies (Cutler et al., 2009; Weisler et al., 2009) and at 150–300 mg/day flexible-dosing monotherapy studies (AstraZeneca Pharmaceuticals D1448C00003; AstraZeneca Pharmaceuticals D1448C00004). Doses of 150 mg/day and 300 mg/day were tested in adjunct therapy studies (Bauer et al., 2009; El-Khalali et al., 2010). In these trials, quetiapine XR demonstrated efficacy across the whole dose range. Quetiapine XR at 100 and 200 mg/day were not tested in these trials, therefore, we may speculate that the starting dose of quetiapine XR may be 50 mg/day and the target dose 300 mg/day. In fact, according to the flexible-dosing study design, quetiapine XR could be increased up to 300 mg/day after 2 weeks of treatment if the patient showed an inadequate response (a failure to achieve ≥20% improvement from randomization in MADRS total score) at their initial dose. Taken together, quetiapine XR dose should be increased up to 300 mg/day based on the clinician's discretion and patient's response. Quetiapine XR was tested in combination with various antidepressants; however, it is not possible to comment on whether one combination is better than another since the subpopulation sample size was not sufficiently large.

5.4. Appropriate time to augment or administer

A prospective failure to current antidepressant was not defined in quetiapine XR studies. This should be principal limitation when comparing adjunct aripiprazole therapy for patients with MDD where partial or non-response was prospectively defined during the study. However, quetiapine XR included a historical failure to ≥1 antidepressant without prospective evaluation during the trials. In the quetiapine XR monotherapy trial, these were not considered but included patients with MDD as a priori inclusion criteria as with the conventional placebo-controlled antidepressant trial. Therefore at least one or more antidepressant failure may deserve quetiapine XR adjunct therapy.

5.5. Well-matched concomitant antidepressant

As previously mentioned, there has been no supporting data as to whether a specific class of individual antidepressant may be significantly superior to a different class or other antidepressant. In the two adjunct RCTs, all antidepressants were used according to approved dose range and quetiapine XR was prescribed as a fixed dose of 150 mg/day or 300 mg/day. Quetiapine XR 300 mg/day showed consistent efficacy compared with 150 mg/day in the two adjunct RCTs (Bauer et al., 2009; El-Khalali et al., 2010). Hence, quetiapine XR may be prescribed regardless of antidepressant type to augment the effect of antidepressants for treating patients with MDD.

5.6. Prudent duration of treatment with quetiapine XR

Quetiapine XR has demonstrated efficacy over placebo in a 52-week maintenance treatment in terms of depression, anxiety, functioning, and medication satisfaction (AstraZeneca Pharmaceuticals D1448C00005). However, health-related quality of life enjoyment and reduction of suicidality were not separated from placebo treatment. According to the STAR*D trial, the importance of reaching remission is highlighted by the lower relapse rates in naturalistic follow-up for patients entering remission compared with those with response but not remission (step 1: 33.5% vs 58.6%; step 2: 47.4% vs 67.7%; step 3: 42.9% vs 76.0%; step 4: 50.0% vs 83.3%) (Rush et al., 2006). Despite the fact that there is no consensus on the duration of augmentation therapy to date, currently available evidence suggest that adjunct aripiprazole may be allowed at least for 1 year, at the discretion of clinicians, with regard to the most appropriate benefit/risk ratio for individual patients (such as effectiveness vs. treatment cost and possibility of EPS, e.t.c.).

5.7. Discontinuation syndrome

Interestingly, 5 of the 6 short-term quetiapine XR RCTs (AstraZeneca Pharmaceuticals D1448C00003; AstraZeneca Pharmaceuticals D1448C00004; Cutler et al., 2009; El-Khalali et al., 2010; Weisler et al., 2009) had a discontinuation phase to assess the withdrawal symptoms after 6–8 weeks of randomized treatment. Among these studies, one trial included duloxetine treatment as an active comparator (Cutler et al., 2009). The most common AEs were nausea and insomnia for quetiapine XR, and dizziness and headache for duloxetine (Cutler et al., 2009). Quetiapine XR was not found to be more significantly associated with a specific one or set of discontinuation symptoms compared with duloxetine or placebo (Cutler et al., 2009). These favorable trends for quetiapine XR over placebo and the active comparators were also seen with the other quetiapine XR RCTs (AstraZeneca Pharmaceuticals D1448C00004; El-Khalali et al., 2010; Weisler et al., 2009).

Currently, any clinical factors relating to differential efficacy for adjunct quetiapine XR, differential effect of adjunct quetiapine XR for treating subgroups of MDD, and efficacy of quetiapine XR for difficult-to-treat populations have yet to be researched.

6. Conclusion

Quetiapine XR may have antidepressant effects through effects on the 5-HT_{2A} receptor, 5-HT_{1A} receptor, glutamate receptor, and norepinephrine transporter. Well-designed and adequately-powered controlled clinical trials (including placebo and/or active comparator) have demonstrated that quetiapine XR has clinically meaningful efficacy and tolerability as monotherapy and adjunct therapy to antidepressants for the treatment of MDD. In such trials, quetiapine XR was generally well tolerated, although some concerns were given to trends for weight gain and metabolic disturbances over the course

of 6–8 and 52 weeks of treatment. However, most cases were mild to moderate and infrequently led to discontinuation.

As of December 2009, the FDA has approved once-daily quetiapine XR as adjunct (add-on) treatment to antidepressants in adults with MDD. Hence quetiapine XR has become the only medication in its class approved by the FDA to treat both MDD as adjunct therapy and acute bipolar depression as monotherapy. In addition, quetiapine XR is currently under review by the FDA as acute monotherapy and maintenance monotherapy for the treatment of MDD in adult patients. However, recent data (Ray et al., 2009) suggesting that taking quetiapine and other atypical antipsychotics doubles the risk of sudden cardiac death. In this study in patients with a variety of psychiatric disorders including schizophrenia, bipolar disorder, MDD or other mood disorder and dementia by Ray and colleagues (2009), 44,218 and 46,089 baseline users of single typical and atypical drugs, respectively, and 186,600 matched non-users of antipsychotic drugs, in which current users of typical and of atypical antipsychotic drugs had higher rates of sudden cardiac death than non-users of antipsychotic drugs, with adjusted incidence-rate ratios of 1.99 and 2.26, respectively (Ray et al., 2009). Long-term risk of patients developing tardive dyskinesia, and in particular metabolic syndrome, also has to be kept in mind in clinical practice (Naber and Lambert, 2009), although in the MDD acute and long-term clinical trials reviewed here no patients reported tardive dyskinesia or metabolic syndrome as side effects.

These AEs may deliver more impact in terms of individual functioning and public health costs to patients with MDD than to patients with schizophrenia (Pae et al., 2008). Hence, quetiapine XR should be considered by clinicians more cautiously after trying currently available and better tolerated first-line treatment options in patients with MDD.

In conclusion, this review highlights that quetiapine XR may have clinical utility in patients with MDD who do not respond or have an inadequate response to previous antidepressant treatment.

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