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Antidepressant Efficacy of the Antipsychotic Quetiapine:Pharmacokinetics, Pharmacodynamics and Clinical Data

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Abstract

Quetiapine (QTP) is an is an atypical antipsychotic, that was approved in 1997 by American Food and Drug Administration (FDA) for schizophrenia, both in adults and adolescents (13-17 years). Since 2003 this drug was approved also for the treatment of maniac episode in bipolar adults and adolescents (10-17 years) then in 2006 FDA extended the use of QTP to bipolar depression episodes and in 2008 to the maintenance treatment of bipolar disorder. In 2009 QTP starts to be used also as add on therapy of major depressive disorder combined to antidepressants, without FDA consent. Actually this drug, in "off label" use, is employed also for monotherapy of unipolar depression.

QTP treatment was generally well tolerated. The incidence of treatment-emergent mania/hypomania was lower with QTP compared with the antidepressant paroxetine and placebo.

Keywords: Antidepressant; Pharmacokinetics; Pharmacodynamics; Clinical data

Introduction

Quetiapine (QTP) is an is an atypical antipsychotic, that was approved in 1997 by American Food and Drug Administration (FDA) for schizophrenia, both in adults and adolescents (13-17 years). Since 2003 this drug was approved also for the treatment of maniac episode in bipolar adults and adolescents (10-17 years) then in 2006 FDA extended the use of QTP to bipolar depression episodes and in 2008 to the maintenance treatment of bipolar disorder [1,2]. In 2009 QTP starts to be used also as add on therapy of major depressive disorder combined to antidepressants, without FDA consent [3]. Actually this drug, in "off label" use, is employed also for others mental diseases like generalized anxiety disorders, monotherapy of unipolar depression, delirium, psychotic symptoms linked to dementia and to obsessive compulsive disorder [4] Therefore from QTP commercialization we can see that it was progressively employed in an increased number of psychiatric diseases not only in those that have obtained the consent of FDA.

For these reason in Europe, The Agency's Committee for Medicinal Products for Human Use (CHMP), after the European Medicines Agency (EMEA) completes the review of the use of QTP and QTP XR, concluded that the knowledge about prescription of this drug in European Union (EU) is too different and so it requires more specific and univocal recommendations. In particular the CHMP confirms that QTP and QTP XR should be used for Schizophrenia and Bipolar Disorder (BD). Concerning BD, CHMP specifies that the drug is allowed only in the treatment of acute manic and depressive episodes and in the prevention of recurrence of manic and depressive episodes that previously responded to quetiapine treatment. The CHMP also recommended that QTP XR can be used in the treatment of Major Depressive Disorder (MDD) only when the response to classical antidepressants was not efficient.

QTP is available in two formulations immediate release (IR) and sustained release (XR) that differ in term of plasmatic peak and clinical effects [5]. Furthermore XR formulation seems to be more comfortable for patients thanking to the once daily administration so the compliance can be better in this case. In particular QTP XR is often used for the treatment of depressive episodes both in Bipolar and Unipolar Disorders even if it is not FDA-approved for the treatment of MDD.

The use of QTP in Affective Disorders is well demonstrated by many double blind, randomized, clinical trials. For these reason QTP is actually one of the most common drug used in bipolar and unipolar disorders [6].

In this review we firstly analysed the pharmacokinetic and pharmacodynamics properties of quetiapine then we take into consideration the pharmacological rationale of the QTP use in unipolar and bipolar depression and finally we describe the RCT studies that showed the effects of QTP, both IR and XR, in depressive episodes of bipolar and unipolar disorders.

Methods

A comprehensive search on PUBMED of all RCTs using quetiapine RI and RP on patients with depressive episodes in unipolar and bipolar disorders published up to December 2015 was performed. Articles of potential interest were identified by using the following search terms: ''quetiapine'', ''quetiapine XR'', ''quetiapine IR'', ''trial'', combined with the following term: "depression", "affective disorder" or "affective symptom" or "mood disorder", ''unipolar'', "bipolar". Among the articles retrieved, RCT studies were identified and screened by reading the abstract and, when necessary, the full text, in order to select those articles relevant for the analysis.

Pharmacology of QTP

Pharmacokinetic profile

QTP is a dibenzothiazepine derivative available both as immediate- release (IR) and extended-release (XR) formulations. When administered in a single dose within the therapeutic range the drug show linear kinetics with an elimination half-life of approximately 7 hours. Both IR and XR formulations provide equal bio availability, however the time to attainment of peak plasma concentration is 5 hours for XR and 2 hours for IR. Higher plasma levels are sustained also for a longer period of time with QTP XR, hence once daily dosing of the XR formulation is required to maintain therapeutic drug concentrations as opposed to IR which needs to be administered at least twice daily [4,5]. QTP is metabolized by the liver into various metabolites with only 1% excreted unaltered in the urine; N-desalkylQTP or norQTP is QTP's most important metabolite. NorQTP is produced by the action of isoenzymes CYP 3A4 in the cytochrome P450 system [6]. Variations in QTP metabolism based on race or genetics are unlikely because of no genetic polymorphisms affect CYP3A4. However, we can find interaction at the level of this isoenzyme with some inductors (carbamazepine, phenytoin) that increase the proportion of norQTP, or with potent enzyme inhibitors (ketoconazole, itraconazole, erythromycin, and fluvoxamine) that slow its production [7,8]. Among older adults and patients with concomitant medications there is more pharmacokinetic variability in the case of QTP than norQTP; this means that norQTP levels are more stable [9].

Minor metabolism occurs via CYP2D6 into 7-hydroxyQTP which is thought not to possess any active properties [10] and into 7-hydroxy-desalkyl-QTP, which is pharmacologically active [11]. According to Mauri et al. [4], QTP's plasma concentrations are not sufficiently high to explain its action at receptors or its clinical effects, suggesting that active metabolites participate in its pharmacodynamic properties. However, the plasma concentrations of Central Nervous System (CNS) drug is a poor predictor of central activity because a lot of other factors can influence target engagement such as blood/brain barrier penetration, CNS accumulation, receptor association/dissociation kinetics. This evidence leads to the view that it is a multifunctional psychoactive drug due to its ability to modify systems of dopaminergic, serotonergic and noradrenergic neurotransmission and its effects appear to be mediated by the actions of both QTP and norQTP [6].

Pharmacodynamic profile

The blockade of dopamine D2 receptors in the mesolimbic pathway could be the main mechanism behind its antipsychotic action. Both QTP and norQTP bind with moderate affinity to D1 and D2 receptors, additionally the former rapidly dissociates from D2 receptors explaining the need of high doses of QTP to bring about its antipsychotic effect [12]. On the other hand, it exhibits low capacity for up-regulation of these receptors, which explains the low incidence of tardive dyskinesia associated with prolonged QTP therapy. In the nigrostriatal and tuberoinfundibular dopamine pathways serotonin acts as an inhibitory modulator by its action on 5HT2A receptor. Both QTP and norQTP strongly antagonize this receptor, thereby facilitating dopamine release in these pathways and resulting in low incidence of extrapyramidal side effects and hyperprolactinemia [13]. Many depressive symptoms such as anhedonia, psychomotor retardation, social withdrawal and loss of motivation result from decreased dopamine neurotransmission in the prefrontal cortex (PFC). It is believed that norQTP with its 5HT2A and 5HT2C antagonism facilitates dopamine release in PFC detecting depressive symptoms in patients with mood disorders [14]. Dopamine reuptake in the PFC is mediated by norepinephrine transporter and norQTP is a strong inhibitor of this transporter, thereby adding another mechanism to the parent drug's antidepressant efficacy [15]. Both QTP and norQTP facilitate serotonergic transmission by behaving as partial agonist at 5HT1A receptors, which are associated with antidepressant and anxiolytic effects in humans. In particular, NorQTP has a high affinity for 5HT1A receptors, similar to buspirone and gepirone. Through this mechanism it increases serotonergic neurotransmission by the raphe neurons in the brain stem as well as modulates 5HT functioning in the limbic and cortical regions [16]. NorQTP also activates the 5HT1A receptors in the hippocampus, this leads to neuron regeneration by increasing the release of trophic factors like the brain-derived neurotropic factor [17]. NorQTP also has a higher affinity for 5HT7 receptor which its involvement in depression and sleep-related, circadian rhythm disorders has been experimentally documented. So norQTP's 5HT7 receptor antagonism contributes to QTP's antidepressant action [18]. NorQTP has been also shown to have a distinct *in vitro* pharmacological profile consistent with a broad therapeutic range and may contribute to the clinical profile of QTP. QTP and norQTP were evaluated using *in vitro* binding and functional assays of targets known to be associated with antidepressant and anxiolytic drug actions, and compared these activities to a representative range of established antipsychotics and antidepressants. NorQTP had equivalent activity to established antidepressants at norepinephrine transporter (NET), while QTP was inactive. NorQTP was active in the mouse forced swimming and rat learned helplessness tests. In *in vivo* receptor occupancy studies, norQTP had significant occupancy at NET at behaviourally relevant doses. Both QTP and norQTP were agonists at 5-HT1A receptors, and the anxiolytic-like activity of norQTP in rat punished responding was blocked by the 5-HT1A

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antagonist. QTP and norQTP have multiple *in vitro* pharmacological actions and results from preclinical studies suggest that activity at NET and 5-HT1A receptors contributes to the antidepressant and anxiolytic effects in patients treated with QTP [19]. NorQTP exhibits distinct pharmacological activity from QTP and plays a fundamental role in its antidepressant efficacy [20]. So it is important to underline that antidepressant activity of QTP is mediated, at least in part, by the active metabolite norQTP, that selectively inhibits noradrenaline reuptake, that it is a partial 5-HT1A receptor agonist, and that it acts as an antagonist at presynaptic α2, 5-HT2C, and 5-HT7 receptors [21].

Unipolar and Bipolar Depression

QTP has a range of clinical activity distinct from other atypical antipsychotic drugs, demonstrating efficacy as monotherapy in bipolar depression, major depressive disorder and generalized anxiety disorder [22]. In fact typical antipsychotics were effective in mania treatment, but can lead to depressive symptoms; so their long term use in BD was frequently discouraged. However many studies suggested that atypical antipsychotics were efficient in the treatment of all phases of BD [23]. Several studies give evidence of efficacy for QTP, aripiprazole and lurasidone in the depressive as well as maintenance phases of BD [24]. These agents are efficient in the treatment of all phases of BD because of their receptor binding properties. Specifically, the affinity for different 5HT receptors plays a crucial role in the mood stabilizing characteristic of these drugs. Similarly to lithium these medications binding to this receptor (5HT) induce secondary changes in the intracellular signal transduction pathways and in the nerve growth factors' activity [25,26]. Studies on the longitudinal course of BD showed that the time spent in depression is more that the time spent in mania [9]. The depressive form could be a major depressive episode, maybe with hospitalization, or chronic sub threshold symptoms with several kinds of symptoms like anxiety, somatic complaints, or effects like substances abuse, eating disorders. So it is very important to find effective treatments for the depressive phase of BD and a number of studies show that QTP monotherapy was an efficacious treatment for acute bipolar depression (BDep). The dosage recommended for depressive episodes associated with BD are 50 mg on day 1, increased to 100 mg on day 2, 200 mg on day 3 and 300 mg on day 4 maximum suggested dose being 300 mg/day. In major depressive disorder QTP is considered as an adjunct to an antidepressant, the initial dose is 50 mg on day 1 and day 2, it is possible increasing to 150 mg on day 3 and day 4, since the recommended daily dosage in the adjunctive therapy of major depressive disorder is 150-300 mg/day [21].

Clinical Data

In this review we examined Randomised Clinical Trials (RCT) and open label studies published in the last thirteen years to update the knowledge about the antidepressive effect of QTP, and indirectly its metabolite theoretically responsible of antianxiety and antidepressant effects, in the treatment of bipolar and unipolar disorders. We considered both monotherapy and combination therapy with QTP.

Sajatovic et al. [27] conducted a study that aimed to compare the efficacy and tolerability of QTP and risperidone for the treatment of depressive symptoms in outpatients with psychosis. In this 4-month, multicenter, open-label trial, patients were randomly assigned in a 3:1 ratio of QTP to risperidone, and both drugs were flexibly dosed. A total of 554 patients were randomly assigned to QTP and 175 to risperidone. Mean doses at 16 weeks were 318 mg for QTP and 4.4 mg for risperidone. Although both agents produced improvements in mean HAM-D scores, QTP produced a greater improvement than risperidone in all patients (p=0.0015). These results could suggest that QTP is useful agent in the management of depressive symptoms in patients with psychosis.

Calabrese et al. [28] conducted a trial of QTP in the treatment of depression in BD. The sample was of five 542 outpatients with bipolar I (N=360) or II (N=182) disorder experiencing a major depressive episode (DSM-IV) were randomly assigned to 8 weeks of QTP (600 or 300 mg/day) or placebo. QTP at higher dose demonstrated statistically significant improvement in Montgomery-Asberg Depression Rating Scale (MADRAS) total scores compared with placebo from week 1 onward. The proportions of patients meeting response criteria at the final assessment in the groups taking 600 and 300 mg/day of QTP were 58.2% and 57.6%, respectively, versus 36.1% for placebo. The proportions of patients meeting remission criteria (MADRAS <or=12) were 52.9% in the groups taking 600 and 300 mg/day of QTP versus 28.4% for placebo. QTP monotherapy demonstrated its efficacy and was well tolerated for the treatment of bipolar depression.

In 2006 Hirschfeld et al. [29], conducted a study for evaluating the effects of QTP monotherapy on anxiety symptoms in bipolar depression. 539 outpatients with bipolar I (N=358) or bipolar II (N=181) disorder experiencing a major depressive episode (DSM-IV) received 8 weeks of QTP monotherapy (600 or 300 mg/day) or placebo. At week 8, QTP 600 and 300 mg/day each demonstrated significant improvements in HAM-A total score versus placebo (p<0.001). In bipolar I depression, QTP showed significant improvement in HAM-A total score versus placebo (p<0.001). In bipolar I depression, QTP also showed significant improvements versus placebo on the HAM-A anxious mood and tension items, HAM-A psychic and somatic subscales, MADRS inner tension item, and HAM-D psychic anxiety item (all p<0.001), but not the HAM-D somatic anxiety item. In bipolar II depression, QTP showed significant improvement versus placebo on the HAM-A anxious mood, MADRS inner tension, and HAM-D psychic anxiety items (all p<0.01). The conclusion was that QTP monotherapy shows efficacy in treating anxiety symptoms in bipolar I depression; however, Authors concluded that the anxiolytic effects in bipolar II disorder required further investigations.

Milev et al. [30], conducted a trial aimed to assess the long-term response of patients with bipolar depression to the addition of QTP to their usual treatment at least 400 mg daily. This study also sought to assess the safety and tolerability of QTP in patients with BD. Data shows that HAM-D scores reduced from 27.2 to 12.1 and CGI scores reduced from 4.7 to 2. The authors concluded that QTP seems to be helpful to and

relatively well tolerated by patients with bipolar depression when it is added to their usual treatment.

In a RCT study Endicott et al. [31] analysed QTP's improvements in quality of life in a sample of 542 patients with bipolar I or II depression to assess the effect of QTP monotherapy, 300 or 600 mg/day, on quality of life. Both doses of QTP significantly improved quality of life over baseline values in comparison with placebo, which was evident at first assessment (week 4) and continued up to week 8. QTP therapy also effected a significant improvement in quality of sleep compared with placebo. Improved quality of life may enhance patient compliance, and assessment of quality of life should be incorporated into future clinical trials in bipolar depression.

Baune et al. [32], investigate the effects of antidepressant therapy plus QTP on MDD focusing on motor activity, daytime sleepiness and quality of sleep. Patients (N=27) with MDD received a standard antidepressant treatment (venlafaxine, escitalopram) plus flexible dose of QTP. Repeated measures of variance indicate an independent influence of QTP on improved depression, motor activity and sleep. Antidepressant treatment plus QTP is possibly a suitable treatment strategy to improve depressive symptomatology.

Del Bello et al. [33], investigated the effectiveness and tolerability of QTP for the treatment of adolescents at high risk for developing Bipolar I Disorder. Mood disorder diagnoses in the adolescents consisted of bipolar disorder not otherwise specified (N=11), dysthymia (N=3), bipolar II disorder (N=3), cyclothymia (N=2), and major depressive disorder (N=1). The majority of patients (N=12, 60%) were non-responders to previous trials of psychotropic agents. 87% of patients were responders (CGI-I <or=2) to QTP at week 12 (mean endpoint dose =460 +/- 88 mg/day). YMRS scores decreased from 18.1 +/- 5.5 at baseline to 8.7 +/- 7.9 at endpoint ($p<0.0001$), and CDRS-R scores decreased from 38.2 +/-9.8 to 27.7 +/- 9.3, ($p=0.0003$). So, the results suggest that QTP may be an effective treatment for mood symptoms in adolescents with a familial risk for developing bipolar I disorder.

Vieta et al. [34], investigated the efficacy and tolerability of QTP monotherapy in patients with Bipolar I or II Disorder with a rapid-cycling disease course. QTP (600 and 300 mg/day) provided significantly greater mean reductions from baseline to week 8 in the MADRS total score than placebo ($p<0.001$) in this sample. Significant improvements were also noted on the CGI, HAM-D, HAM-A, Pittsburgh Sleep Quality Index, and Quality of Life Enjoyment and Satisfaction Questionnaire scales. So QTP monotherapy (600 or 300 mg/day) is clinically effective and well tolerated in the short-term treatment of depressive episodes in patients with BD I e BD II who have a rapid-cycling disease course.

Suppes et al. [22], investigated the efficacy and tolerability of QTP monotherapy for depressive episodes in patients with BD II; they analysed data from two RCT. A post-hoc evaluation was conducted in 351 patients with BP II depression combined from two RCT 8-week studies of QTP (300 or 600 mg/day) that included depressed patients affected by BD I e BD II. The primary endpoint was change from baseline to week 8 in MADRS total score. In patients affected by BD II, improvement in mean MADRS total score from baseline was significantly greater with QTP 300 (n=107) and 600 mg/day (n=106) from the first assessment (week 1) through week 8 compared with placebo (n=108). Change in HAM-D, HAM-A, and CGI were also significantly greater for QTP groups versus placebo. QTP demonstrated significant efficacy as monotherapy, compared with placebo, for the treatment of acute depressive episodes in BD II.

Similarly Weisler et al. [35], investigated the efficacy and tolerability of QTP monotherapy for the treatment of depressive episodes in patients with BD I, as a post hoc analysis of data from the BipOLar DEpRession (BOLDER) I and II studies, which both investigated the overall efficacy of QTP in both bipolar I and II disorder. In the combined cohort of patients with depressive episodes in BD I, there was significantly greater clinical improvement in mean MADRS total scores among patients who received QTP compared with placebo from baseline to week 1 and through week 8. QTP monotherapy (300 and 600 mg/day) is more effective than placebo and generally well tolerated for the treatment of depressive episodes in patients with BD I.

Duffy et al. [36], examined the effectiveness and tolerability of QTP as a maintenance treatment preventing against relapse or recurrence of acute mood episodes in adolescent patients diagnosed with BD. Of the 21 enrolled patients, 18 completed the 48-week study. 13 patients could be maintained, without relapse or recurrence, in good quality remission on QTP monotherapy, while 5 patients required additional medication to treat impairing residual depressive and/or anxiety symptoms. Neurocognitive test performance over treatment was equivalent to that of a matched healthy control group. QTP was generally well tolerated with no serious adverse effects. This study suggests that adolescents patients diagnosed with BD can be successfully maintained on QTP monotherapy.

In 2010 another RCT study by Suppes et al. [37] evaluated the effectiveness of QTP extended release once daily in bipolar depression. The subjects were acutely depressed adults with BD I and BD II, with or without rapid cycling. Patients were randomized to 8 weeks of QTP XR 300 mg daily monotherapy or placebo. The results showed that QTP XR 300 mg once daily (n=133) showed significantly greater improvement in depressive symptoms compared with placebo (n=137) from week 1 through to week 8. Mean change in MADRS total score at week 8 was −17.4 in the QTP XR group and −11.9 in the placebo group ($p<0.001$). Response (≥ 50% reduction in MADRS total score) and remission (MADRS total score ≤ 12) rates at week 8 were significantly higher with QTP XR compared with placebo. QTP XR improved core symptoms of depression. The study concluded that QTP XR (300 mg) once daily monotherapy was significantly more effective than placebo for treating episodes of depression in BD.

Young et al. [38], data compared the efficacy and tolerability of QTP and lithium monotherapy with that of placebo for a major depressive episode in BD and the results showed that the mean MADRS total score change from the baseline at 8 weeks was −15.4 for QTP 300 mg/day, −16.1 for QTP 600 mg/day, −13.6

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for lithium, and −11.8 for placebo. QTP 600 mg/day was significantly more effective than lithium in improving MADRS total score at week 8. QTP treated but not lithium treated, patients showed significant improvements (p0.05) in MADRS response and remission rates, HAM-D, Clinical Global Impressions-Severity of illness and -Change, HAM-A scores at week 8 versus placebo. Both QTP doses were more effective than lithium on the HRSD and HAM-A at week 8. The study concluded that QTP (300 or 600 mg/day) was more effective than placebo for the treatment of acute episodes of depression in BD. Lithium did not differ significantly from placebo on the main measures of efficacy.

Mc Elroy SL et al. [39], data evaluated the efficacy and tolerability of QTP and paroxetine monotherapy for major depression in BD and the results showed that the mean MADRS score change from baseline at 8 weeks was −16.19 for QTP 300 mg/day, −16.31 for QTP 600 mg, −13.76 for paroxetine, and −12.60 for placebo. QTP treated (both doses) patients showed significantly greater improvement ($p \leq 0.05$) in most secondary outcome measures at week 8 versus the placebo group. Both QTP doses were associated with greater improvement than paroxetine for MADRS and HAM-D scores. The incidence of treatment-emergent mania/hypomania was lower with QTP compared with paroxetine and placebo. The conclusions were that QTP (300 or 600 mg/day), but not paroxetine, was more effective than placebo for treating acute depressive episodes in BD I and BD II. QTP treatment was generally well tolerated.

Ketter et al. [40], wanted to assess QTP effectiveness in BD patients in a clinical setting. Mean QTP duration and final dose were 385 days and 196 mg/day (50.0% of patients took a dosage of 75 mg/day). In 38.5% of trials QTP was continued on average 328 days with no subsequent psychotropic added. In 22.9% QTP was continued on average 613 days, but had subsequent psychotropic added after on average 113 days, most often for depressive symptoms. Aside from sedation, QTP was generally well tolerated. They concluded that in BD outpatients QTP had a moderate (38.5%, with 385-day mean duration) discontinuation rate, and commonly did not require subsequent additional pharmacotherapy, suggesting effectiveness in a clinical setting.

Weisle et al. [35], investigated the efficacy and safety of QTP monotherapy as maintenance treatment in BD I compared with switching to placebo or lithium. Patients aged 18 years with DSM-IV-diagnosed bipolar I disorder and a current or recent manic, depressive, or mixed episode received open-label QTP (300-800 mg/d) for 4-24 weeks. Patients achieving stabilization were randomized to continue QTP or to switch to placebo or lithium (0.6-1.2 mEq/L) for up to 104 weeks in a double-blind trial. Of 2,438 patients starting open-label QTP, 1,226 (50.3%) were randomized to double-blind treatment, including 1,172 (95.6%) in the intent-to-treat population. Time to recurrence of any mood event was significantly longer for QTP and lithium versus placebo ($p<0.0001$). QTP and lithium significantly increased time to recurrence of both manic events and depressive events ($p<0.004$) compared with placebo. In patients stabilized during acute QTP treatment, continuation of QTP significantly increased time to recurrence of any mood, manic, or depressive event compared with switching to placebo. Switching to lithium was also more effective than placebo for the prevention of manic and depressive events.

Kim et al. [41], compared the effect of QTP XR with lithium on depressive symptoms and sleep in bipolar depression patients during 8 weeks of trial. A total of 42 patients with bipolar depression were screened out. In both groups, HAM-D scores were significantly decreased and remission rate in the QTP XR was significantly higher than that of the lithium group. In the QTP XR group, PSQI scores at weeks 1, 2, 4, 6, and 8 was significantly decreased compared with baseline. Sleep efficiency at weeks 6 and 8 was significantly increased. The wake after sleep onset (WASO) at week 8 was significantly decreased. QTP XR monotherapy was more effective in treating bipolar depression than lithium. In particular, QTP XR treatment improved both subjective and objective sleep quality in patients with bipolar depression.

A recently published meta-analysis [42-45] systematically reviewed the efficacy and tolerability of QTP either as monotherapy or adjunctively to mood stabilizers in the treatment of acute bipolar depression. The number of patients included in these 11 RCTs was 3,488 and two of the trials were conducted in children and adolescents (ages 10 to 18). The change in depression scores was significantly greater in the QTP group compared with the placebo group. The significant difference was observed from week 1 on clinical global impression, quality of life, sleep quality, anxiety and functioning. The more important trials only on QTP monotherapy in bipolar depression are reported in Table 1.

Table 1: Trials on quetiapine monotherapy in Bipolar Depression; Pt: Patients; N°: Number of patients; BP: Bipolar Disorder; Pb: Placebo; wks: weeks.

Study	Patients: diagnosis and N	Treatment	Study Duration (weeks)	Treated Patients (N) and dosages	Pb (n)	Primary outcome	Remission Rate Treatment	Remission Rate Pb
Calabrese et al. (BOLDERI)	BP I: 360 BP II: 182	QTP 300-600 mg/day *vs.* PB	8	180: 300 mg 181: 600 mg	181	Change in MADRAS	53%	28%

Thase et al. (BOLDER II)	BP I: 338 BP II: 171	QTP 300-600 mg/day *vs.* PB	8	172: 300 mg 169: 600 mg	168	Change in MADRAS	52%	37%
McElroy et al. (EMBOLDEN II)	BP I: 478 BP II: 262	QTP 300-600 mg/day *vs.* PB and *vs.* paroxetine 20mg	8	245: 300 mg 247: 600 mg 122: 20 mg	126	Change in MADRAS	69% (greater improvement than paroxetine)	55%
Young et al. (EMBOLDEN I)	BP I: 499 BP II: 303	QTP 300-600 mg/day *vs.* PB and *vs.* lithium	8	265: 300 mg 268: 600 mg 136: 600-1800 mg	133	Change in MADRAS	70% (More effective than lithium)	55%
Suppes et al.	BP I: 107 BP II: 26	QTP 300-600 mg/day *vs.* PB	8	139	137	Change in MADRAS	54%	39%

Tolerability

QTP treatment was generally well tolerated. A great number of studies did not report significant change in body weight; although in clinical experience a certain weight gain was observed. No any extrapyramidal or anticholinergic side effects of note were reported.

There are few studies of comparison with antidepressants. Mc Elroy et al. [39] conducted a double-blind placebo controlled study evaluating tolerability of QTP and paroxetine monotherapy for major depression in BD. The most common adverse events were dry mouth, somnolence, sedation and dizziness with QTP at the dosages of 300 and 600 mg/die and dry mouth, sedation, headache, insomnia and nausea with paroxetine.

The incidence of treatment-emergent mania/hypomania was lower with QTP compared with paroxetine and placebo. A higher weight increase (≥7%) was observed in both quetiapine groups (9 and 11% respectively) compared with paroxetine (3%) and placebo groups (4%). Regarding laboratory parameters no significant changes over 8 weeks of treatment with QTP were observed although higher mean changes in insulin and triglyceride levels from baseline to last assessment were observed among patients in QTP and placebo groups compared with paroxetine group.

Conclusions

QTP is a multifunctional psychoactive drug due to its ability to modify dopaminergic, serotonergic and noradrenergic neurotransmission and its effects appear to be mediated by the actions of both the mother drug QTP, but in particular by its active metabolite, norQTP.

QTP monotherapy seems to be effective in acute bipolar depression also in the view of prevention of mania/hypomania switching and this data represents an advantage in respect to antidepressant monotherapy. By demonstrating the effectiveness of QTP monotherapy over placebo and the antidepressant paroxetine there are valuable evidences to support the use of the drug as a first line opportunity for the acute and maintenance treatment of bipolar depression. The common practice to use antidepressants often as monotherapy to treat BD I and particularly BD II depressed patients should be considered with great attention and caution by clinicians [46]. On the other hand QTP treatment was generally well tolerated.

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