The use of atypical antipsychotics beyond psychoses: efficacy of quetiapine in bipolar disorder

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Background and rationale: Atypical antpsychotics have been sucessfully used in the treatment of bipolar disorder (BD), either as adjunctive or as monotherapy. Quetiapine is an atypical antipsychotic extensively used in the treatment of psychotic disorders. It has serotonergic and dopaminergic activity and it appears to be selective for the mesolimbic and mesocortical dopamine system. The aim of this paper was to review the recent literature on the use of quetiapine in the treatment of BD.

Methods: The literature databases currently available online were searched for papers on quetiapine and BD. Papers and reports published between January 1995 and June 2005 were selected and reviewed critically.

Results: Augmentative low dose quetiapine was found to be effective in BD partially responsive to conventional mood-stabilizers. Manic and mixed episodes have been the best studied, and quetiapine was found to be effective either as monotherapy or as adjunctive therapy in both randomized clinical trials and open-label studies. Data on the use of quetiapine in bipolar depression showed a significant efficacy and high remission rates. Maintenance data suggested a role of quetiapine as a good alternative to classical mood stabilizers in reducing recurrence rates of BD. A few studies on the efficacy in rapid cycling BD have also been published.

Conclusions: Quetiapine is an effective agent for the short- and long-term treatment of BD. The mechanism of action of quetiapine as a mood stabilizer is still unknown. Some preliminary data suggest the involvement of glutamate pathways but further studies are needed to clarify this issue.

Keywords: bipolar disorder, treatment, atypical antipsychotics, quetiapine

Introduction

Atypical antipsychotics are useful in the management of patients with schizophrenia and other psychotic disorders. These agents are as effective as conventional antipsychotics, such as haloperidol or chlorpromazine, but they have a different clinical profile in schizophrenia (ie, better efficacy on negative symptoms) and an overall better safety profile, being associated with a lower risk of inducing extrapyramidal side-effects (Yatham 2003).

More recently there has been increasing evidence for the utility of atypical antipsychotics in the treatment of bipolar disorder (BD), either as adjunctive therapy (in combination with classical mood stabilizers) or as monotherapy (Berk and Dodd 2003).

The addition of antipsychotics to mood stabilizers results in a more rapid onset of action and in a better control of agitation and psychotic behavior during manic episodes of BD (Alderfer and Allen 2003). However, even though

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neuroleptics are effective antimanic agents, these compounds show little or no efficacy on depressive symptoms (Yatham 2003). In addition, neuroleptics may induce secondary depressive symptoms and their use in the long-term treatment of BD is usually discouraged (Yatham 2003).

Several studies suggest that atypical antipsychotics are effective not only in the treatment of acute mania (Tohen et al 2000; Keck et al 2003a; Khanna et al 2003) but also in the management of other phases of BD. Olanzapine monotherapy is as effective as classical mood stabilizers in the maintenance treatment of BD (Altamura et al 2004), and the combination of olanzapine and fluoxetine as well as olanzapine monotherapy have been found to be more effective than placebo in the treatment of acute bipolar depression (Tohen et al 2003). More recent studies suggest that risperidone, aripiprazole, and quetiapine may be also effective in the long-term maintenance treatment of BD and in bipolar depression (Ketter et al 2004; Vieta and Goikolea 2005).

Thus, atypical antipsychotics appear to have a significant clinical effect in any phase of the treatment of BD, but the exact mechanism underlying their mood-stabilizing properties is still unknown.

It has been hypothesized that the antimanic effect is related to dopamine receptor blockade, while the anti-depressant effect is related to the blockade of serotonin 5-HT$_2$ receptors (Vieta 2005). However, no hypotheses exist on the mechanism of action of atypical antipsychotics in preventing recurrences of BD in the long-term course of the illness.

BD shares some clinical features with schizophrenia, and both schizophrenia and BD may have a common biological (Manji and Lenox 2000) and/or genetic background. It may be hypothesized that several genes confer susceptibility to psychoses, and that the psychosis will be phenotypically expressed as schizophrenia or BD depending on the presence of other genetic or environmental factors (Kasper et al 2002). On the other hand, BD has a clinical peculiarity, which is not shared by schizophrenia or other psychotic disorders. BD, as well as other mood disorders, is recurrent and cyclic and the neurobiological basis of this clinical characteristic is still not completely unraveled.

Even though atypical antipsychotics may have similar efficacy on BD symptoms, they appear to be heterogeneous. Different atypical antipsychotics have different pharmaco-dynamic, pharmacokinetic, and clinical profiles and thus they may be indicated for different patients with BD (Vieta and Goikolea 2005).

The aim of the present study was to review the recent literature on the use of quetiapine in the treatment of BD with the intent of drawing a clinical efficacy profile of this compound for the use in BD (see Table 1). Papers on the pharmacological properties of quetiapine were also reviewed and commented upon.

Pharmacology
Pharmacodynamic properties

Atypical antipsychotics act by modulating different neurotransmission systems and their pharmacological profile implies not only the blockade of dopaminergic receptors (Kane 1996).

Quetiapine fumarate is a dibenzothiazepine derivative with both serotonergic and dopaminergic activity. This compound has a moderate affinity for 5-HT$_{2A}$, adrenergic (α_1), muscarinic, and histaminergic H$_1$ receptors, a minor affinity for dopamine D$_2$ and 5-HT$_{1A}$ receptors, and very low affinity for 5-HT$_{2C}$, α_2, and D$_1$ receptors (DeVane and Nemeroff 2001). Its pharmacological effects appear to be selective for the mesolimbic and mesocortical dopamine pathways, while effects on the nigrostriatal dopamine pathway, which is involved in the induction of extra-pyramidal side-effects (EPS), are minimal (Goldstein 1999). For this reason quetiapine shows placebo-level incidence of EPS, which are not dose-dependent (Arvanitis and Miller 1997). Quetiapine shows a reduced activity on dopamine receptors of the tuberoinfundibolar system, thus preventing the induction of hyperprolactinemia, in common with neuroleptics and with some atypical antipsychotics (Goldstein 1999).

The good tolerability profile of quetiapine particularly with respect to the increase in prolactin plasma levels has been explained also by a "dynamic" observation. The dissociation between central and peripheral dopamine D$_2$ receptor occupancy appears to be a major determinant of the degree of prolactin elevation during antipsychotic treatment at therapeutic doses. Quetiapine shows a rapid dissociation from dopamine D$_2$ receptors (Garver 2000) and a lower pituitary versus striatal D$_2$ occupancy when compared with antipsychotics with a propensity for prolactin elevation (Kapur et al 2002).

No relationship between quetiapine plasma levels and clinical response was found. Thus, in clinical practice,

Table 1 Summary of the main clinical studies investigating the efficacy of quetiapine as adjunctive or monotherapy in the treatment of BD

Study	Illness phase	Quetiapine daily dose	Add-on	Study duration	Comparison/ adjunctive	Efficacy
Sokolski and Denson (2003)	Manic or mixed	173 ± 157 mg	yes	retrospective study	Li VP	Li/VP + QTP > Li/VP
Vieta et al (2005)	Manic	up to 800 mg	no	12 weeks	PBO haloperidol Li	QTP > PBO QTP = Li = haloperidol
Sachs et al (2004)	Manic	504 mg	yes	3 weeks	PBO Li DVP	QTP + Li/DVP > PBO + Li/DVP
Yatham et al (2004)	Manic	100–800 mg	yes	3 weeks/6 weeks	PBO Li DVP	QTP + Li/DVP > PBO + Li/DVP
Bahk et al (2004)	Manic	25–200 mg	yes	4 weeks	VP Li Li+VP Li+CBZ	QTP + Li/VP/Li + VP/Li + CBZ > Li/VP/Li + VP/Li + CBZ
DelBello et al (2002)	Manic or mixed	432 mg	yes	6 weeks	PBO DVP	QTP + DVP > PBO + DVP
Calabrese et al (2004)	Depressive	300 mg or 600 mg	no	8 weeks	PBO	QTP > PBO
Altamura et al (2003)	Maintenance	157.7 ± 157.6 mg	no	12 months	VP Li gabapentin	QTP = VP = Li = gabapentin
Pae et al (2005)	Maintenance	204.1 ± 78.1 mg	yes	24 weeks	VP Li CBZ topiramate	QTP + VP/Li/CBZ/ topiramate > VP/Li/CBZ/topiramate

Abbreviations: CBZ, carbamazepine; DVP, divalproex; Li, lithium; PBO, placebo; QTP, quetiapine; VP, valproate.

monitoring plasma concentration is not necessary for adjusting the dosage (Small et al 1997).

Metabolic disturbances, including obesity, dyslipidemia, and diabetes mellitus, are common adverse events during antipsychotic treatment (Nasrallah and Newcomer 2004). The mechanisms underlying these side-effects are not well understood. It has been hypothesized that they are mediated by the decrease in serotoninergic 5-HT_{2A} and 5-HT_{2C} signaling, which influence appetite and food intake, physical activity, and metabolic rate (Wirshing et al 1998; Melkersson et al 2000). The report of a recent consensus development conference on antipsychotics drugs suggests that the risks of obesity, diabetes, and hyperlipidemia with quetiapine are intermediate, being less than with clozapine and olanzapine, but more than with ziprasidone and aripiprazole. Weight

gain is a relatively common side-effect with some antipsychotics; in quetiapine monotherapy trials, the mean weight gain was 1.8 kg after 12 weeks' treatment (Vieta et al 2005); during treatment with olanzapine in schizophrenic patients, a weight gain of 4.2 kg was observed after 10 weeks (Allison et al 1999). On the other hand, no significant weight gain was reported for aripiprazole (Lyseng-Williamson and Perry 2004) or ziprasidone (Keck et al 2003b).

Patients treated with quetiapine, compared with those treated with aripiprazole or ziprasidone, are the least susceptible to develop akathisia, while sedation is the main side-effect of the treatment with quetiapine (Vieta and Goikolea 2005). Moreover, this compound has not been associated with congenital malformations in humans (FDA Pregnancy Category C) (Ketter et al 2004).

Pharmacokinetic properties

After quetiapine oral administration the mean time needed to reach maximum plasma concentrations (t_{max}) ranges from 1 to 1.5 hours; food intake does not modify the absorption of quetiapine. The binding with plasma proteins is about 83%. For low doses (10–25 mg) quetiapine plasma levels decline, with a mean apparent elimination half-life ($t_{1/2}$) ranging from 3.1 to 5.5 hours. For doses of 250 mg and higher, the mean $t_{1/2}$ is approximately 6 hours. Quetiapine is primarily and extensively metabolized. Plasma concentrations of the two active metabolites, 7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine, are about 5% and 2%, respectively, of those of quetiapine. Quetiapine appears to be the major circulating species in plasma and its metabolites do not contribute to the pharmacological effects of the mother drug (DeVane and Nemeroff 2001). The enzyme primarily responsible for the metabolism of quetiapine is CYP3A4, while a small contribution is given by CYP2D6 (Grimm et al 1997). Approximately 73% of the drug is excreted in the urine and 21% in feces.

There are no gender-related differences in the pharmacokinetics of quetiapine, and no dose adjustment is required when treating adolescent (McConville et al 2000) or elderly patients.

Unlike what has been shown with other antipsychotics, quetiapine metabolism is not affected by cigarette smoking, given that CYP1A2, the major CYP enzyme induced by cigarette smoking, is not involved in quetiapine metabolism.

A study on a small sample (n = 8) of nonpsychotic individuals with renal or hepatic impairment has been done to determine the effect of these dysfunctions on quetiapine pharmacokinetics. The changes observed in quetiapine kinetics suggest that in patients with liver dysfunction the standard starting dosage may be given and the dosage escalation should be conducted with caution. No relationship was found between renal function and quetiapine clearance (Thyrum et al 2000).

Drug interactions

The coadministration of phenytoin (a potent inducer of CYP3A4) and quetiapine may accelerate the metabolism of quetiapine and reduce its efficacy; therefore in patients receiving both drugs, increased dosages of the antipsychotic may be required to maintain control of psychotic symptoms (Wong et al 2001). An adjustment of quetiapine dosage is also necessary during treatment with thioridazine, because this drug increases the clearance of quetiapine (Potkin et al

2002). On the other hand, the coadministration of ketoconazole, a potent inhibitor of the CYP3A4 enzyme system, decreases quetiapine clearance.

Clinical use of quetiapine in BD

The main goals of the pharmacological management of BD are 1) to treat manic or mixed episodes; 2) to treat depressive episodes; 3) to avoid switching into mania during antidepressant-treatment; and 4) to prevent relapses and recurrences in the long term. Conventional mood stabilizers, such as lithium and anticonvulsants, have represented the first-choice treatment for BD (Altamura et al 2004). However, classical mood stabilizers may have a limited clinical efficacy during severe manic phases, bipolar depression, or maintenance treatment, have a low therapeutic index, and may require frequent plasma levels determinations to avoid toxicity or adverse events (Berk and Dodd 2005). The atypical antipsychotic quetiapine, as augmentation therapy in BD patients with partial response to classical mood stabilizers, was found to be effective and well tolerated (Dunayevich and Strakowski 2000; Sajatovic et al 2001). A retrospective study, conducted to evaluate the effect of adjunctive quetiapine, included 16 patients with bipolar I disorder (9 were in a mixed episode and the others were manic) who were on monotherapy with lithium or valproate for a minimum of 3 months prior to quetiapine initiation. BD symptoms were evaluated using the Clinical Global Impression Scale for severity of bipolar illness (CGI-BP, Spearing et al 1997), at baseline and at endpoint after quetiapine dose had been stable for at least 1 month. Considering CGI-BP severity scores, the addition of quetiapine resulted in a significant improvement in mania, depression, and overall bipolar illness. Quetiapine efficacy was particularly evident on insomnia, psychomotor agitation, depressed mood, elevated mood, racing thoughts, irritability, impulsivity, pressured speech, hypersexuality, and psychosis (Sokolski and Denson 2003).

An important issue for the use of quetiapine in the treatment of BD is the choice of the optimal dose. Manic patients should be administered high doses in the early phases of the treatment, and doses may be later adjusted and reduced. On the other hand, depressed patients appear to be responsive to lower doses (Vieta et al 2002).

Manic episodes and mixed states

Most of the data on the use of atypical antipsychotics, including quetiapine, in BD come from studies done on

patients treated during manic or mixed episodes. To date, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole have been approved for the use in bipolar mania by the US Food and Drug Administration, while olanzapine, risperidone, and quetiapine have been approved by the European Medicines Agency (Vieta and Goikolea 2005).

The primary aim in the treatment of mania is to control symptoms rapidly, minimizing side-effects. Current guidelines recommend the use of lithium or valproate with the addition of an antipsychotic in severe manic episodes, while mild to moderate episodes could be treated with monotherapy (antipsychotic, lithium, or valproate) (APA 2002).

Quetiapine was found to be an effective antimanic agent either as monotherapy or as combination therapy in addition to classical mood stabilizers in randomized clinical trials and open-label studies (Keck 2005).

Two clinical trials on the effect of quetiapine monotherapy for the treatment of acute bipolar mania have been conducted (Bowden et al 2005; McIntyre et al 2005). Each trial was a 12-week, multicenter, double-blind, placebo-controlled study on bipolar I disorder patients included during manic episodes. Patients were randomized to be administered quetiapine (up to 800 mg/day) or placebo. Two additional groups of subjects received lithium or haloperidol. In a combined analysis of these studies, quetiapine appeared to be superior to placebo in reducing Young Mania Rating Scale (YMRS) baseline scores from day 4 to day 84, and to be equivalent to haloperidol or lithium in reducing YMRS scores by day 84. However, considering tolerability profiles these agents significantly differed. The quality of these two studies, when compared to that of previous studies, is enhanced by the inclusion of an active comparator in addition to placebo group (Vieta et al 2005).

The efficacy and tolerability of quetiapine as add-on treatment was evaluated in a 3-week, double-blind, placebo-controlled study, done on BD I (manic phase) patients. Subjects included in the study were treated with lithium or valproate semisodium, and were randomized to be administered adjunctive quetiapine (up to 800 mg/day) or placebo. Assessments included a complete medical and psychiatric history, the administration of the YMRS and of the CGI-BP Severity of Illness, a complete physical examination, vital signs, weight, blood chemistry testing, thyroid function test, and ECG. Additional treatments allowed during the study were lorazepam, zolpidem, chloral hydrate, or zaleplon. Reduction in YMRS scores and in CGI-BP severity scores, from baseline to week 3, was

significantly higher in the quetiapine-treated group than in the placebo-treated one. In addition, the number of subjects who achieved remission at the end of the study was significantly higher among patients who received quetiapine. Moreover, adjunctive quetiapine did not appear to precipitate depressive symptoms (Sachs et al 2004).

Data obtained from this study and data obtained from another large, randomized, 6-week, double-blind study have been analyzed jointly. Since the two studies were carried out under identical protocols, combined analyses of data of these 402 patients were performed. The analysis showed a significantly greater reduction in YMRS scores and in CGI-BP severity of illness scores in patients receiving quetiapine plus lithium or divalproex than in those receiving lithium or divalproex monotherapy. These results indicate that quetiapine, when used in combination with lithium or divalproex, is more effective in controlling manic symptoms than either lithium or divalproex monotherapy (Yatham et al 2004).

An open-label, 4-week study investigated the short-term efficacy of quetiapine in addition to mood stabilizers for the treatment of adult patients with acute manic or hypomanic episodes during the course of BD I. This study included 18 patients treated with quetiapine added to lithium, valproate, lithium and valproate, or lithium and carbamazepine. YMRS, CGI, Hamilton Rating Scale for Depression (HDRS), and the Brief Psychiatric Rating Scale (BPRS) were used to evaluate the efficacy of this add-on therapy. YMRS, HDRS, BPRS, and CGI scores were significantly reduced at the endpoint in the quetiapine add-on groups (Bahk et al 2004).

Another study on the efficacy of quetiapine in manic or mixed episodes has been done on 30 adolescents with BD (Del Bello et al 2002). Subjects, treated with divalproex, were randomized to quetiapine or placebo. At the end of the observation period, patients assigned to quetiapine presented with significantly lower YMRS scores and a better response rate than patients assigned to placebo.

Depressive episodes

The efficacy of quetiapine as mood stabilizer was initially observed in studies done on patients treated for the presence of psychotic symptoms. A meta-analysis of data from three clinical trials that examined the use of quetiapine in patients with schizophrenia showed a reduction of the severity of symptoms commonly observed also in BD, ie, anxiety, depression, apathy, thought disturbances, motor activation, and hostility (Borison et al 1996; Arvanitis and Miller 1997;

Small et al 1997). A 4-month, multicenter, open-label trial that included patients with different psychotic disorders randomized to quetiapine or risperidone, suggested the utility of quetiapine for the management of depressive symptoms (Sajatovic et al 2002). Purdon and colleagues (Purdon et al 2001) showed that quetiapine, when compared with haloperidol, was more effective in reducing depressive symptoms in schizophrenic patients.

The effect of quetiapine on depressive symptoms is supported by the results of a large, multicenter, randomized, double-blind, placebo-controlled trial that assessed the efficacy of quetiapine monotherapy in subjects with DSM-IV diagnosis of BD I or BD II. A total of 542 patients, with moderate or severe bipolar depression (based on the Montgomery-Asberg Depression Rating Scale [MADRS] scores), were randomized to receive quetiapine (300 mg or 600 mg/day) or placebo for 8 weeks. At week 1 quetiapine-treated patients showed a significant improvement on MADRS total score when compared with placebo-treated patients. This improvement in depressive symptoms continued throughout the treatment period, until the end of the study. Similar results were observed when analyzing HDRS scores. The clinical response and the rates of remission were also significantly higher in the group of patients treated with quetiapine (Calabrese et al 2004). Moreover, "core" depressive symptoms, anxiety symptoms, and suicidal ideation were also improved during quetiapine treatment (Calabrese et al 2004; Macfadden et al 2004).

Maintenance treatment

To date, less data are available on the use of atypical antipsychotics in the maintenance therapy of BD than on the use of these compounds in the treatment of manic or mixed episodes. However, several open-label and double-blind trials suggest that atypical antipsychotics may reduce relapse and recurrence rates during long-term therapy, either alone or in combination with conventional mood stabilizers.

The two monotherapy studies that led to the approval of the use of quetiapine in acute mania were of 12 weeks' duration (Vieta et al 2005). This treatment period was long enough to allow for a more sustained assessment of efficacy, particularly in terms of evaluating remission and response rates (Vieta and Goikolea 2005). Another study, although preliminary, considered longer treatment duration and thus it may be considered the first long-term study on the use of quetiapine monotherapy in BD. In this study, 28 BD outpatients were included and followed up for 12 months

(Altamura et al 2003). Subjects were randomly assigned to quetiapine or to a classical mood-stabilizer (valproate, lithium, or gabapentin) and were assessed at baseline and every 2 months until the end of the study. Assessment included the administration of BPRS, CGI, YMRS, and HDRS. Considering both psychopathology and global functioning measures, quetiapine appeared to have an efficacy comparable to that of conventional mood stabilizers, with a favorable tolerability profile.

In another open-label study, patients with BD I were treated with quetiapine, in combination with standard therapy, for a period of 76 weeks. The addition of quetiapine induced a significant reduction in the relative risk of developing manic or depressive relapses (Carta et al 2004).

An additional study evaluated the efficacy of quetiapine as adjunctive therapy in the long-term treatment for bipolar mania. The study was done on 23 patients with BD I, and the clinical evaluation included the administration of YMRS, CGI, and HDRS and was done at baseline and at weeks 1, 4, 12, and 24 (endpoint). The significant reductions of the YMRS, CGI, and HDRS scores pointed out the efficacy of add-on quetiapine in the long-term treatment of BD (Pae et al 2005).

Rapid cycling BD

Patients with a rapid-cycling course of BD usually show poor or no response to classical mood stabilizers (Calabrese et al 2001). The main goal of pharmacological treatment in rapid- cycling BD patients is to reduce the cycle frequency and to improve the long-term outcome (Vieta 1999). The clinical guidelines of the American Psychiatric Association endorse the use of mood stabilizer plus antipsychotic combinations as first-line treatment in subjects with severe rapid-cycling disease (APA 2002). However, few studies exist on the efficacy of pharmacotherapy on the long-term course of rapid-cycling BD, and polypharmacy is often the only way to obtain euthymia (Post et al 1998).

A small open-label study was done on 14 rapid-cycling BD patients treated with add-on quetiapine to the original psychotropic regimen of each patient. The concomitant treatments were benzodiazepines, antidepressants (ie, venlafaxine, paroxetine, clomipramine, or mirtazapine) or mood-stabilizers (ie, lithium, valproate, carbamazepine). At the beginning of the study 5 subjects were manic, 2 were hypomanic, 1 was euthymic, 3 were depressed, and 3 were in a mixed state. Patients were followedup for 112 ± 33 days and the efficacy of quetiapine addition was evaluated using

the CGI-BP, YMRS, and HDRS. An overall improvement of 2 of the 3 CGI-BP subscales (the general subscale and the manic subscale) and of the YMRS was observed. This result suggests that quetiapine may be an effective treatment for rapid-cycling BD patients (Vieta et al 2002).

Another open-label study, conducted by Ghaemi and colleagues (Ghaemi et al 2002), showed the efficacy and tolerability of quetiapine in 16 rapid-cycling BD subjects. In this study both mania and depressive scores decreased significantly from baseline to the end of the observation period.

Quetiapine-induced mania

An important consideration when treating patients with BD is the risk of inducing switching into mania or hypomania. The pathogenesis of drug-induced mania in BD is complex, probably including also genetic susceptibility factors. However, the phenomenon is a serious complication of BD treatment both in the short- and in the long-term management of the illness (Mundo et al 2001). Despite the fact that several studies have shown that quetiapine is effective in controlling acute mania, there are some recent case reports of manic symptoms associated with quetiapine treatment (Biancosino et al 2003; Lykouras et al 2003; Pacchiarotti et al 2003). As has been hypothesized for risperidone-induced mania, the switching may be caused by high $5\text{-HT}_{2A}/D_2$ receptor occupancy (Lane et al 1998; Richelson 1999; Schmidt et al 2001), even though individual susceptibility factors cannot be excluded and rather are likely to play a substantial role. It is worth mentioning that all cases with mania or hypomania induced during quetiapine treatment remitted soon after quetiapine dose reduction (Rachid et al 2004).

Conclusions

Published data on the use of quetiapine in BD show that it is a safe and effective compound for the treatment of acute episodes, as either augmentative therapy or monotherapy. Most of the studies have pointed out the comparable efficacy of quetiapine on manic or mixed episodes to that of classical mood stabilizers, with the advantage of a better tolerability profile and a higher therapeutic index. More recent data on the use of quetiapine monotherapy (Calabrese et al 2004) in the treatment of bipolar depressive episodes appear to be more interesting. These data, although promising, need further replication on additional samples.

Controlled studies on the use of quetiapine monotherapy in the maintenance treatment of BD are still few.

It has been shown that quetiapine is as effective as valproate, lithium, or gabapentin in reducing recurrence rates in BD episodes, with an overall better tolerability.

Quetiapine, as well as other atypical antipsychotics such as olanzapine, appear to have a specific effect on BD compared with neuroleptics. Neuroleptics have a proven effect on manic symptoms (Bourin et al 2005; Smulevich et al 2005) but no positive effects on depressive episodes (Altamura 1996; Bourin et al 2005) or on the prevention of recurrences (Esparon et al 1986). On the other hand, atypical compounds (ie, olanzapine, quetiapine) have been shown to act on any phase of BD and also on the long-term maintenance phase of the illness (Altamura et al 2003, 2004).

The mechanism of action of atypical antipsychotics as antimanic or antidepressant agents has been explained by the fact that these compounds block dopamine D_2 and serotonin 5-HT_2 receptors. These pharmacological properties have been associated with the antimanic and the antidepressant effects, respectively (Vieta 2005). Moreover, these two receptor subtypes have been implicated in the pathogenesis of quetiapine-induced manic switches reported in a few case reports (Biancosino et al 2003; Lykouras et al 2003; Pacchiarotti et al 2003).

However, the mechanism of action of quetiapine or olanzapine as long-term mood stabilizers in preventing recurrences of BD is still unknown.

With respect to the pharmacological properties of these two compounds, it has been shown by preclinical studies that olanzapine and quetiapine, but not typical antipsychotics, may have an effect on the expression of glutamate receptors. Chronic administration of quetiapine, but not of haloperidol, reduces the expression of ionotropic and metabotropic glutamate receptors in rat brain, particularly in the nucleus accumbens (Tascedda et al 1999). In addition, chronic olanzapine administration up-regulates glutamate AMPA receptors in the frontal cortex of rat brain, while haloperidol has no effect (Tascedda et al 2001). More recently, clinical studies on schizophrenia patients have shown that the treatment with some atypical antipsychotics (ie, quetiapine, olanzapine, risperidone, sertindole) induces an increase in glutamate plasma levels that is not correlated with the clinical antipsychotic response (van der Heiden et al 2004). What makes these studies interesting for the understanding of the possible mechanisms of action of atypical antipsychotics as long-term mood stabilizers in BD is that the glutamate system has been implicated in the pathogenesis of BD itself. This evidence comes from some

genetic studies suggesting that polymorphisms of the glutamate receptor genes are implicated in the pathogenesis of BD (Mundo et al 2003). In addition, the neurobiological model of recurrence for mood disorders, including BD, involves glutamate receptors (Post & Weiss 1999).

The hypothesis that atypical antipsychotics act as mood stabilizers through their effect on the glutamate system, and the intriguing convergence of data on the potential involvement of glutamate in the pathogenesis of BD, warrant new biological and clinical research in the field.

Finally, data on the significant clinical effect of quetiapine in reducing recurrence rates in rapid cycling BD, although preliminary, appear to be interesting.

In conclusion, the efficacy of quetiapine in treating different phases of BD has been supported by several studies, even though for some of them further replications and more detailed results are needed.

Further studies should investigate the relationship between quetiapine dose and antidepressant response together with the effect of quetiapine not only on "core" depressive symptoms but also on anxiety symptoms and on suicidal ideation. In addition, it would be useful to investigate specifically the potential effects of atypical antipsychotics, including quetiapine, in reducing or increasing manic switch rates. When treating bipolar depression the use of antidepressant monotherapy is considered a risk factor for antidepressant-induced mania, and mood stabilizers have been found to be protective with respect to this side-effect (Mundo et al 2006). However, there are no controlled studies investigating differences or similarities between atypical antipsychotics and classical mood stabilizers in preventing induction of manic switches or rapid-cycling course in bipolar patients.

Also, future studies on clinical subtypes of BD characterized by high rates of comorbidities, worse outcome, and poor response to classical mood stabilizers are needed, as well as studies aimed at defining the specific profile of BD patients who may preferentially respond to atypical antipsychotics and quetiapine.

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