Early onset of action and sleep-improving effect are crucial in decreasing suicide risk: the role of quetiapine XR in the treatment of unipolar and bipolar depression

Azione precoce ed effetto di miglioramento del sonno sono cruciali nel ridurre il rischio di suicidio: il ruolo della quetiapina XR nel trattamento della depressione unipolare e bipolare

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SUMMARY. Although the possibilities of antidepressive pharmacotherapy are continuously improving, the rate of nonresponders or partial responders is still relatively high. Suicidal behavior, the most tragic consequence of untreated or unsuccessfully treated depression, commonly observed in the first few weeks of antidepressive treatment before the onset of therapeutic action, is strongly related to certain symptoms of depression like insomnia. The present paper reviews the newly discovered and well-documented antidepressive effect of quetiapine in bipolar and unipolar depression with special focus on its early onset of action and its sleep-improving effects. Both beneficial effects play an important role in the reduction of suicidal risk frequently observed in depressed patients.

KEY WORDS: quetiapine, major depression, insomnia, suicide, side effects.

RIASSUNTO. Anche se le possibilità, in termini di terapia farmacologica antidepressiva, sono in continuo miglioramento, i tassi di non-responder o responder parziali sono ancora relativamente elevati. Il comportamento suicidario, la conseguenza più tragica della depressione non trattata o trattata con scarso successo, comunemente osservata nelle prime settimane del trattamento antidepressivo prima della comparsa dell'azione terapeutica, è fortemente legato ad alcuni specifici sintomi della depressione, come l'insonnia. Il presente studio esamina l'effetto antidepressivo, recentemente scoperto e ben documentato, della quetiapina nel disturbo bipolare e nella depressione unipolare, con un focus specifico sulla rapidità d'azione e sugli effetti di miglioramento sul sonno. Entrambi gli effetti benefici della quetiapina svolgono un ruolo importante nella riduzione del rischio suicidario frequentemente osservato nei pazienti depressi.

PAROLE CHIAVE: quetiapina, depression maggiore, insonnia, suicidio, effetti collaterali.

INTRODUCTION

Suicidal behavior is a complex phenomenon often resulting from the interplay of many factors. One model (1) proposed a stress-diathesis combination in the precipitation of a suicidal act. A stressor such as a psychiatric disorder or a psychosocial crisis may lead to suicidal ideation; if the individual has specific personality traits, vulnerability due to genetic, biology and early traumatic experiences a suicidal act becomes most probable. A typical stressor includes the acute worsening of a psychiatric disorder, but often an acute psychosocial crisis seems to be the most proximal stressor. In a study of suicide attempters versus non-at-

tempters, attempters reported significantly more adverse life events both in the last 6 months, and between the ages of 0-15 years than non-attempters (2).

Unbearable psychological pain conceptualized as psychache (3), comprehends the hurt, anguish, or ache that takes hold in the mind; the pain of excessively felt shame, guilt, fear, anxiety, loneliness, angst, dread of growing old or of dying badly. Although Shneidman (4) admits that each suicide is a multifaceted event, that biological, cultural, sociological, interpersonal, intrapsychic, logical, philosophical, conscious, and unconscious elements are always present, he suggests that the essential nature of suicide is psychological, meaning that each suicidal drama occurs in the mind of a unique individual. Insomnia, agitation, and inner tension are clinical features usually associated with the perturbated state of mind in subjects with increased suicide risk. It is well-known that the prospect of improvement for depressive patients greatly increases with the careful and informed application of Selective Serotonin Reuptake Inhibitors (SSRIs) and other new antidepressants (dual action agents, and agomelatine) (5-7), and about 50-60% of patients shows a marked improvement or reaches remission after the first or second antidepressant trial due to the presence of residual symptoms (8). However, at the same time around 25-30% of patients shows only minimal (clinically insufficient) improvement during the first two antidepressant trials. Therefore clinicians often need to try a third antidepressant or to apply combination or augmentation strategies (9-11), or to use auxiliary sleep improving/anxiolytic medications. However, these therapeutic approaches are usually only applied during the 8-12th week of treatment, while depressive symptoms persist or only partially improved. It is also well-known that a long major depressive episode increases suicide risk and worsens the prospective for further improvement (12,13), while clinically relevant remission during the early phase of therapy (at the end of the second week) is a reliable predictor of full remission (14). Although suicide is a complex, multicausal phenomenon with multiple cultural and psychosocial background factors, untreated or refractory depression is a contributing factor in the precipitation of attempted or completed suicide (12,15,16). At the same time, in patients with major depressive episode suicide or suicide attempt is a relatively frequently event during the first weeks of antidepressive therapy (especially during the first ten days), when antidepressants do not yet exert full action (15,17). In a study by Jick et al. (17) in unipolar major depressive patients, 55% of suicides within the first 90 days of initiating antidepressant pharmacotherapy took place during the first 9 days of therapy, which means a 5-fold increased frequency compared to the equal distribution of suicides in ten day-intervals. It is also often observed that if bipolarity is unrecognized or hidden antidepressive monotherapy without mood stabilizing agents worsens depression and agitation especially in the first weeks of treatment and, less frequently, induces suicidal behavior (18). This increased suicidal risk is associated with some of the more prominent symptoms of the disorder: insomnia, hopelessness, agitation/comorbid increased anxiety, lack of appetite weight reduction (12,19-22) and apathy, a primary deficit in motivation that most of the time coexists with depression (23). Insomnia, a distressing condition which makes everyday life unbearable in addition to the other symptoms of depression such as hopelessness, agitation, lack of appetite, and weight reduction is a an important risk factor for suicide (12,19-22), especially if "nightmares" are also present (24). Sleep problems (in the majority of cases insomnia) are the most frequent and earliest symptoms of depression (16), which has an equally marked significance for treatment, prevention of relapse and suicidal behavior. Therefore during pharmacotherapy, early onset of action, an improvement in sleep and anxiolytic effect play an important role not only in earlier improvement of depressive symptoms but also in suicide prevention. We have seen that in depressed patients, suicide risk is especially high in the first days or weeks when the antidepressant action has not been manifested yet (15,17). At the same time, it has been shown that in patients responding well to antidepressant therapy the risk of suicide markedly decreases in parallel with improvement of depressive symptoms (12,16,25,26).

The rate of responders and remitters is 5-20% higher when patients are treated with dual action antidepressants (duloxetine, venlafaxine) (27-30) and escitalopram and agomelatine, compared to some SSRIs (fluoxetine, fluvoxamine, paroxetine). The onset of antidepressant action is also earlier (in about a week) (31-39). In the past decade there is increasing evidence that in contrast to classical (typical) antipsychotics, atypical antipsychotics may also possess antidepressive and mood stabilizing properties in addition to their well known antipsychotic and antimanic effects.

METHODS

In order to provide a new and timely critical overview of quetiapine XR in the treatment of unipolar and bipolar depression with particular regard to early onset of action and sleep-improving effect as crucial aspects in decreasing

suicide risk we performed a detailed PubMed/MedlineMedLine, MedicaScopus, PsycLit, PsycInfo search to identify all papers and book chapters in English language during the period between 1980 and August 2012.

The search used a combination of the following terms: "Quetiapine" AND "Major Depressive Disorder" OR "MDD" OR "Major Depression" AND "Bipolar Depression" AND "efficacy" AND "Safety" AND "Tolerability" AND "Suicide" OR "Suicidal behaviour" OR "Suicide attempts" OR "Suicidal ideation" OR "Suicidality". Where a title or abstract seemed to describe a study eligible for inclusion, the full article was examined to assess its relevance based on the inclusion criteria. Two independent researchers conducted a two-step literature search. Any discrepancies between the two reviewers who, blind to each other, examined the studies for the possible inclusion were resolved by consultations with a senior author. The reference lists of the articles included in the review were also manually checked for relevant studies.

ATYPICAL ANTIPSYCHOTICS AS ANTIDEPRESSANTS

Olanzapine was the first atypical antipsychotic demonstrated to possess antidepressant effects in bipolar I major depression, and phase prophylactic effect in bipolar I manic patients besides its antipsychotic and antimanic effects (40,41). In an 8-week, randomized, double blind, placebo controlled study of more than 800 patients Tohen et al. (40) found a significantly higher rate of responders and remitters in the group treated with a combination of olanzapine and fluoxetine (responders: 56%, remitters: 49%) compared to placebo (responders: 30%, remitters: 24%).

Since quetiapine therapy is effective in reducing depressive symptoms in schizophrenia (42), several studies investigated the possible antidepressive effect of quetiapine in bipolar depressions. In an 8-week, randomized, placebo-controlled study of more than 540 patients with major depressive episode (360 bipolar I and 182 bipolar II, BOLDER I study), quetiapine IR monotherapy (300 or 600 mg/day) produced response and remission rates of 58%-58%, and 53%-53%, respectively, while the same figures in the placebo group were 36% and 28%. Mania occurred in 3.2% of patients receiving quetiapine IR and in 3.9% of patients receiving placebo (43). In the BOLDER II study of 509 patients with the same design similar results were obtained (rate of responders and remitters: quetiapine IR monotherapy 300 mg/day or 600 mg/day= 60% and 52%, 52% and 52% respectively; placebo= 45% and 37%). The MADRS response and remission rates were significantly greater in both quetiapine dose groups compared with placebo. Hypomanic or manic switch occurred in 3% of patients in the quetiapine IR group and 7% of patients in the placebo group (44). Besides the definitive antidepressive effect of olanzapine-fluoxetine combination and quetiapine IR monotherapy in bipolar depression, in recent years there have been several promising reports with regard to the use of other atypical antipsychotics (e.g. risperidone, aripiprazole, ziprasidone) in the acute and long-term treatment of mood disorders and especially bipolar disorder (45,46). A detailed review of these findings goes beyond the scope of this paper.

ANTIDEPRESSIVE EFFECT OF QUETIAPINE XR IN BIPOLAR DEPRESSION AND ITS ROLE IN TREATING INSOMNIA

Based on the current literature quetiapine represents a safe and effective short and long-term pharmacological option in the treatment of bipolar depression (47). All most recent guidelines for the treatment of acute bipolar depression recommended quetiapine as a first-line option (48-51).

Both quetiapine monotherapy and combination with additional mood stabilizers may be useful in the prophylaxis of depressive episodes (48).

Quetiapine and its active metabolite, norquetiapine is an antagonist of D2, and 5-HT1A and 5-HT2A receptors and norquetiapine has a marked noradrenaline reuptake inhibitory action (characteristic of tricyclic and dual action antidepressants) (52).

Patients with bipolar depression type I showed greater improvement on the MADRS compared to those with bipolar depression type II. Treatment of hypomanic symptoms frequently present in bipolar I and II plays a role in the mechanism of action (16,18,53). Also, individuals with a rapid-cycling disorder demonstrated a general improvement in depressive symptoms, irrespective of bipolar course. Quetiapine XR has been recently suggested as a valuable first-line treatment for bipolar depression (48).

Vieta et al. (54) found that maintenance treatment with quetiapine combined with lithium/divalproex significantly increased time to recurrence of any event (mania, depression, or mixed) regardless of the polarity of the index episode when compared with placebo and lithium/divalproex. Patients received open-label quetiapine at flexible doses (400-800 mg/day) combined with lithium or divalproex for up to 36 weeks obtained at least 12 weeks of clinical stability. They were later randomized to double-blind treatment with quetiapine (400-800 mg/day) plus lithium/divalproex or

placebo plus lithium/divalproex for other 104 weeks. They concluded that quetiapine with lithium/divalproex may provide an effective long-term treatment option for bipolar I disorder to prevent recurrences not only of mania but also depression. Later, some other relevant studies (EMBOLDEN I and II) also investigated the efficacy of quetiapine in the treatment of acute bipolar depression.

Young et al. (55) in a 8-week study including 802 patients (499 with a bipolar disorder type I and 303 with a bipolar disorder type II) randomly assigned to quetiapine (300 or 600 mg/day), lithium 600-1800 mg/day or placebo found that quetiapine 600 mg/d was significantly more effective in improving MADRS total score at week 8 when compared to lithium. Patients who were treated with quetiapine (300 or 600 mg/day), but not those who were treated with lithium or placebo, significantly improved in MADRS, Hamilton Depression Rating Scale (HDRS), Clinical Global Impressions-Bipolar-Severity of Illness Hamilton Anxiety Rating Scale responses and remission rates. Most importantly, there was an important improvement in the suicide thoughts, inner tension and insomnia which are the symptoms often associated with increased suicide risk. It is of interest to note that lithium only mildly reduced suicide thoughts as measured with the MADRS.

McElroy et al. (56) in the EMBOLDEN II study, a 8-week placebo-controlled study conducted on 740 patients (478 bipolar I, 262 bipolar II) with major depressive episodes who were randomly assigned to quetiapine 300 or 600 mg/day, paroxetine 20 mg/day or placebo reported that both quetiapine doses were associated with greater improvements in MADRS and HDRS total scores when compared with paroxetine or placebo.

Patients treated with quetiapine (300 and 600 mg) significantly improved on MADR item 3 (inner tension), item 4 (reduced sleep), item 5 (reduced appetite), and particularly item 10 (suicidal thoughts) with 600 mg when compared with paroxetine (20 mg). However, the number of patients recruited in the quetiapine groups, was almost twice than that in the paroxetine group; therefore, the paroxetine group may have been less powered to detect differences from placebo when compared with the quetiapine groups.

Patients treated with paroxetine and placebo were more likely to report a treatment-emergent mania/hypomania than those treated with quetiapine. Quetiapine treatment was generally well tolerated in both studies. Again, there was an important statistically significant reduction in suicide thoughts, inner tension and insomnia whereas paroxetine did not report any important action on such features.

The efficacy and safety of quetiapine (400-800 daily dose) adjunctive to lithium or divalproex was also investigated in the recurrence of mood events in a total sample of 1953 patients for up to 36 weeks (57). Overall, 628 subjects who were clinically considered as stable after 12 weeks of treatment were then randomly allocated to double-blind treatment with quetiapine or placebo combined with both lithium or divalproex for other 104 weeks. A small percentage of paients in the quetiapine group (20.3%) reported a mood event when compared with the placebo group (52.1%). Hazard ratios were 0.30 for manic and 0.33 for depressive events, respectively. Individuals treated with quetiapine showed more frequent sedation, weight gain, and hypothyroidism than those with placebo.

Quetiapine may be also useful for the continuation and maintenance treatment of bipolar disorder (58,59). Overall, this drug has been suggested to be a well-established pharmacological option for the treatment of bipolar depression (60).

Oversedation should be managed as one of the most relevant obstacles compromising the use of quetiapine in acute phase of bipolar depression (51). Also, the effect of quetiapine in treating insomnia cannot be ignored considering its moderately sedative properties. Antidepressive and antisuicidal effects of quetiapine in bipolar and unipolar depression with special focus to its early onset of action and its sleep-improving effects have recently been reviewed by Rihmer (61). The use of atypical antipsychotic agents such as quetiapine has been suggested particularly to treat severe insomnia or to lessen agitation that frequently disrupts sleep (62). Todder et al. (63) suggested that quetiapine showed a significant improvement in both subjective and objective sleep parameters. Particularly, significant improvements were reported regarding total sleep time, sleep efficiency, and subjective sleep scores and also changes in rapid eye movement and percentage of rapid eye movement sleep in different populations (64). However, some authors suggested that the role of quetiapine for improving sleep in various patient populations is uncertain and some of the mentioned results may not be clinically significant (64). There has been insufficient research and trials evaluating low-dose quetiapine for the treatment of insomnia are generally limited by the small sample size and the short duration (65). Also, as recently suggested, benefits and harms are vary among atypical antipsychotics for off-label usage. Based on pooled analysis of three large trials, quetiapine was also found to be associated with a 26 percent greater likelihood of "responding," defined as at least 50 percent improvement on the Hamilton Anxi-

ety Scale when compared with placebo in the treatment of generalized anxiety disorder (66). Finally, quetiapine has been recognized as a well-documented pharmacological agent for the treatment of bipolar depression as well as it successfully used in the treatment of insomnia although there are no clinical trial data to support its later use. As suggested by Foral et al. (67), further additional studies are required in order to define the role of second- and third-line pharmacological agents in the management of insomnia.

ANTIDEPRESSIVE EFFECT OF QUETIAPINE XR IN UNIPOLAR MAJOR DEPRESSION

Following the proved efficacy of quetiapine IR monotherapy in bipolar I and II depression, the authors set out to investigate whether there is a similar marked antidepressant effect in unipolar major depression. In a study in 38 centers in the United States between April 2006 and May 2007 (Diamond study) the authors compared the effect of quetiapine XR (extended release) 150 mg/day and 300 mg/day, with duloxetine (60 mg/day) and placebo. In the study, 612 non-psychotic, non-suicidal patients diagnosed with DSM-IV unipolar major depression were randomized into one of the four arms, and 442 (72%) patients completed the 6-week study. The rates of responders at the end of the 6 weeks were 54.4%, 55.1%, 49.6% and 36.2% in the quetiapine XR 150 mg, quetiapine XR 300 mg, duloxetine 60 mg and placebo groups, respectively, and the difference was significant in case of all active treatment groups compared to placebo. Rate of remission at the end of 6 weeks was also significantly higher in the quetiapine XR 150 mg, quetiapine XR 300 mg, and duloxetine 60 mg groups (38.1%, 39.5%, 39.0%, respectively) compared to placebo (27.6%). The decrease in mean MADRS scores was significantly higher in the two quetiapine XR groups already on the 8th day (8.4, 8.2) compared to the duloxetine (6.8) and placebo (6.1) groups (52).

In contrast to patients receiving duloxetine and placebo, in those patients receiving quetiapine XR 150 mg therapy there was a significant decrease in MADRS "depressed mood", "insomnia" and "suicidal ideation" items already on day 8 (52). The patients tolerated the active treatments well, adverse side effects were encountered relatively rarely; dry mouth, drowsiness and sedation were more frequent in patients receiving quetiapine XR, while headache, constipation and sexual dysfunction was more frequent in patients receiving duloxetine therapy. Extrapyramidal side effects were also rare (quetiapine XR 150 mg and 300 mg: 4.6% and 5.3% respectively), and similarly rare was weight increase (mean weight increase: quetiapine 150 mg= +1.0 kg, quetiapine 300 mg= +1.3 kg, duloxetine 60 mg= - 0.5 kg, placebo= 0.1 kg) (38). ECG alterations (including increased QT interval) were not observed in any patients. Beyond the well-known antipsychotic and antimanic effect of quetiapine (42,45,68) the above controlled studies indicate that quetiapine IR and quetiapine XR are effective and safe treatments for bipolar I and II depression, and quetiapine XR also in unipolar major depression.

The efficacy of extended release quetiapine fumarate (quetiapine XR) combined to antidepressant treatment had been also investigated in a pooled analysis of two randomised, placebo-controlled studies. Bauer et al. (69) found that quetiapine XR (150 or 300 mg/day) was effective in reducing MADRS total scores when compared to placebo at both week 1 and 6. Quetiapine XR (150 or 300mg/day) showed a broad efficacy irrespective of concomitant antidepressant treatment and placebo, significantly improving MADRS responses and remission rates. Specifically, quetiapine XR 300 mg/day significantly improved observed and reported sadness, inner tension, reduced sleep, inability to feel, pessimistic thoughts and suicidal thoughts at week 6 of treatment.

Furthermore, in a 11-week (9-week randomized; 2-week posttreatment phase), double-blind, placebo-controlled, Phase III study on 338 elderly patients with major depressive disorder, quetiapine XR monotherapy (50-300 mg/day, flexibly dosed) was found to be effective in improving depressive symptoms, with symptom improvement observed as early as week 1 (70).

Similarly, in a pooled analysis of two 6-week, randomized, double-blind, placebo-controlled studies conducted on 968 outpatients with major depression, quetiapine XR (150 and 300 mg/day) monotherapy reduced depressive symptoms, with significant improvements compared with placebo from week 1 onward. The therapeutic effect of quetiapine XR was neither limited to nor driven by factors such as sex, age, or severity of depression (71).

In addition, another 10-week (8-week active treatment phase and 2-week drug-discontinuation/tapering phase), multicenter, parallel-group, placebo-controlled, double-blind, randomized, Phase III study was conducted to test efficacy and tolerability of quetiapine XR monotherapy in 310 patients initially received quetiapine XR 150 mg/day or placebo. The authors reported that quetiapine XR monotherapy may be effective in patients with major depression, with symptom improvement observed as early as week 1 (72).

The incidences of scores ≥4 with MADRS Item 10 at week 6 were 0.6% when using quetiapine XR 150 mg/day, 1.0% when using quetiapine XR 300 mg/day and 2.6% with placebo and the only two patients who discontinued treatment due to the emergence of adverse events potentially related to suicidality were taking quetiapine XR 150 mg/day and placebo, respectively (in this later case the placebo-treated patient had an adverse event related to a severe suicide attempt on day 2 of treatment). The authors concluded that quetiapine XR was effective in patients with major depressive disorder and with an inadequate response to antidepressant treatment determining an early and general improvement in depressive symptoms. With regard to suicide risk reduction, there was an improvement in the suicide thoughts, inner tension and insomnia.

Similarly, El-Khalili et al. (73) evaluated the efficacy of quetiapine XR as adjunctive therapy in patients with MDD having an inadequate response to ongoing antidepressant treatment. The authors recruited 446 patients who were later randomized to quetiapine XR 150 mg/day, 300 mg/day, or placebo together with the ongoing antidepressant treatment in a 8-week multicentre, double-blind, placebo-controlled study. A significant improvement was observed with quetiapine XR 300 mg/day vs. placebo in terms of MADRS total score at week 1; MADRS response and remission rates; Hamilton Depression Rating Scale (HAMD) and Clinical Global Impression-Severity of illness (CGI-S) changes at week 6. However, patients who were administered quetiapine XR 150 mg/day did not significantly improve vs. placebo, with the exception of MADRS and HAMD total scores (at weeks 1-2 and at week 6, respectively). As in the other studies the improvement of insomnia, suicide thoughts and inner tension may be considered important for reducing suicide risk.

Furthermore, several open label clinical studies found quetiapine augmentation to be effective in therapy resistant depression (74,75). In another recent, open-label, naturalistic study 50-600 mg quetiapine (mean: 340 mg/day) in addition to antidepressants (escitalopram, mirtazapine, sertraline) produced significantly faster improvement and significantly higher remission rates compared to antidepressant monotherapy in unipolar agitated major depression (76).

The advantageous antidepressive effects of quetiapine (including early onset of action, anxiolytic and agitation reducing effect) mean more than a new perspective in the treatment of depression, they are also useful in preventing depression-related suicides, since – as we already mentioned in the introduction – suicidal behavior during antidepressive treatment occurs most frequently in the first weeks of therapy, and mostly in patients with insomnia and agitation/anxiety (12,15,17, 19,22).

However, a secondary pooled analysis performed on data from two studies evaluating the efficacy of once-daily quetiapine XR monotherapy in 968 patients with major depression (of which 788 (81.4%) were classified as anxious depressed based on HAMD anxiety/somatization factor score ≥7 and 180 (18.6%) were nonanxious) demonstrated that quetiapine XR monotherapy improves depressive symptoms irrespective of whether patients have major depression with high or low levels of anxiety (77).

Besides its antimanic and antidepressive effect, quetiapine seems to have a long-term phase prophylactic effect in bipolar I and II patients especially when combined with classical mood stabilizers. In an open-label, long-term follow-up study Altamura et al. (78) found that at the end of year 4, 80% of patients in the quetiapine+lithium group, and 78% of patients in the quetiapine+valproate group did not relapse, while the same ratios were 29%, 46%, 42% and 33% for patients receiving quetiapine, lithium, lamotrigine and valproate monotherapy, respectively.

Quetiapine XR administered at flexible dose (150-300 mg/day) was also reported to significantly improve menopause-related symptoms in 40 midlife women with major depressive disorder based on results of a 2-week, placebo lead-in phase, followed by an 8-week open trial. Spoecifically, the authors found that 17 subjects may be considered as responders (>50% reduction in MADRS scores) and 15 achieved remission (MADRS <10) (79).

Finally, it's important to note that a timely assessment of suicidal risk may be considered of critical relevance in research and clinical settings with psychiatric patients and, particularly, with patients with major depressive disorders. Suicidal risk is difficult to assess and no single psychological test is sufficiently sensitive and specific to use in suicide assessment.

Many psychometric instruments measuring suicidal risk exist, they may be also combined to assess subjects at suicidal risk in clinical practice. Among all, the Gotland Scale of Male Depression may be considered a valid instrument for measuring non-typical ("suicidality-related") symptoms of depression in both male and female patients (80) as well as the Suicide History Self-Rating Screening Scale which was considered a valid and reliable tool for assessing suicide risk (81).

CONCLUSIONS

Quetiapine may be successfully used to treat bipolar disorder and unipolar major depression and may

have antisuicidal properties. Also, quetiapine may exert an early onset of action and relevant sleep-improving effects, being an interesting psychopharmacological option in those bipolar and unipolar patients with a refractory insomnia. However, the mechanism of action of quetiapine as well as its potential is not yet fully understood. Further large-scale, long-term studies including multiple comparisons between various classes of antidepressants are needed in order to investigate the beneficial properties of this drug.

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