Antidepressive efficacy of quetiapine XR in unipolar major depression – The role of early onset of action and sleep-improving effect in decreasing suicide risk

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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 develops in the first few weeks of antidepressive treatment before the onset of therapeutic action and is strongly related to certain specific 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 regards to its early onset of action, and its sleep-improving effects. Both beneficial effects play an important role in the reduction of suicidal risk frequently seen in depressed patients.

Keywords: mirtazapine, major depression, insomnia, suicide, side-effects

It is well-known that the prospect of improvement for depressive patients greatly increases with the careful and informed application of SSRIs and other new antidepressants (dual action agents, and escitalopram or agomelatine), and about 50-60% of patients shows a marked improvement or reaches remission after the first or second antidepressive trial. However, at the same time around 25-30% of patients shows only minimal (clinically insufficient) improvement with the first two antidepressant trials. Therefore clinicians often need to try a third antidepressant or apply combination or augmentation strategies (Kornstein and Schneider, 2001; Jefferson, 2008; Papakostas et al., 2008), or auxiliary sleep improving/anxiolytic medications. These therapeutic approaches however are usually only applied during the 8-12th week of treatment, while depressive symptoms persist or are only partially improved. It is also well-known that a permanently present depressive episode increases suicide risk and worsens the prospective for further improvement (Rihmer, 2007; Altamura et al., 2008a), while clinically relevant remission during the early phase of therapy (at the end of the second week) is a reliable predictor of full remission (Henkel et al., 2009).

Although suicide is a complex, multicausal phenomenon with several cultural and psychosocial background factors, untreated or permanently present depression is the most frequent cause of attempted or completed suicide (Simon et al., 2006; Goodwin and Jamison, 2007; Rihmer, 2007). At the same time, in case of major depressive episode (the most common risk factor for suicidal behavior) 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 (Jick et al., 2004; Simon et al., 2006). In a study by Jick et al., (Jick et al., 2004) in unipolar major depressive patients, 55% of suicides within the first 90 days of initiating antidepressant pharmacotherapy happened 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 in case of unrecognized or hidden bipolarity antidepressive monotherapy without mood stabilizing agents worsens depression and agitation especially in the first weeks of treatment and, more rarely, induces suicidal behavior (Rihmer and Akiskal, 2006). 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 and weight reduction (Fawcet et al.,

1990; Paffenbarger et al., 1994; Taylor, 2003; McGirr et al., 2007; Rihmer, 2007). Insomnia, a distressing condition which makes everyday existence unbearable also beyond the other symptoms of depression (besides hopelessness, agitation, lack of appetite, and weight reduction) is a an important risk factor for suicide (Fawcet et al., 1990; Paffenbarger et al., 1994; Taylor, 2003; McGirr et al., 2007; Rihmer, 2007), especially if "nightmares" are also present (Agargun et al., 2007). Sleep problems (in the majority of cases insomnia) are the most frequent and earliest symptoms of depression (Goodwin and Jamison, 2007), which has an equally marked significance for treatment, prevention of relapse and suicidal behavior. Therefore during pharmacotherapy, early onset of action and sleep improving 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 case of depressed patients suicide risk is especially high in the first days or weeks when the antidepressant action has not been manifested yet (Jick et al., 2004; Simon et al., 2006), at the same time it is proven that in patients responding well to antidepressant therapy the risk of suicide shows a marked decrease in parallel with improvement of depressive symptoms (Goodwin and Jamison, 2007; Rihmer, 2007; Tondo et al., 2008; Zisok et al., 2009).

The rate of responders and remitters is 5-20% higher in pharmacotherapy with dual action antidepressants (duloxetine, mirtazapine, venlafaxine) and escitalopram and agomelatine, compared to some SSRI antidepressants (fluoxetine, fluvoxamine, paroxetine), and the onset of antidepressant action is also earlier (about a week) (Benkert et al., 2000; Kent et al., 2000; Quitkin et al., 2001; Almasi and Rihmer, 2004; Kasper et al., 2006; Gartlehner et al., 2008a, 2008b; San and Arranz, 2008). 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 effect.

ATYPICAL ANTIPSYCHOTICS AS ANTIDEPRESSANTS

Olanzapine was the first atypical antipsychotic demonstrated to possess acute antidepressant effects in bipolar I major depression, and phase prophylactic effect in bipolar I manic patients besides its well known antipsychotic and antimanic effect (Tohen et al., 2003, 2006). In an 8-week, randomized, double blind, placebo controlled study of more than 800 patients Tohen and colleagues 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%) (Tohen et al., 2003). Since quetiapine therapy is effective in reducing depressive symptoms in schizophrenia (Tendon, 2004), several studies investigated the possible antidepressive effect of quetiapine in major 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 (Calabrese et al., 2005). 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%). Hipomanic or manic switch occurred in 3% of patients in the quetiapine IR group and 7% of patients in the placebo group (Thase et al., 2006).

Besides the definitive antidepressive effect of olanzapine-fluoxetine combination and quetiapine IR monotherapy in bipolar depression, in recent years there are several positive and promising reports for using other atypical antipsychotics (e.g. risperidone, aripiprazole, ziprasidone) in the acute and long-term treatment of mood disorders and especially bipolar disorder (Fountoulakis and Vieta, 2008; Liebowitz et al., 2009), however, a detailed review of these findings is beyond the scope of the recent paper.

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 if 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 was randomized into one

Table 1. Quetiapine XR 150 mg, quetiapine XR 300 mg, duloxetine 60 mg and placebo inDSM-IV unipolar major depression (Diamond study, Cutler et al., 2009)

	Quetiapine-150	Quetiapine-300	Duloxetine 60	Placebo
Randomized, n	152	152	149	157
Completed study, n (%)	100 (66)	113 (74)	105 (70)	124 (79)
Mean age, years	42,3	40,9	41.6	40,2
MADRS*, mean, initial	29,8	30,1	30,4	30,3
MADRS, mean, decrease at week 6	14,8	15,3	14,3	11,2
MADRS, mean, decrease at day 8	8,4	8,2	6,8	6,1
Responders at week 6, %	54,4	55,1	49,6	36,2
Remitters ** at week 6, %	38,1	39,5	39,0	27,6

* MADRS = Montgomery-Asberg Depression Rating Scale
** Remitter: MADRS total score of ≤10 at week 6

of the four arms, and 442 (72%) patients completed the six-week study. The rate of responders at the end of the 6 weeks was 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 six 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 (Cutler et al., 2009, see also Table 1).

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 (Cutler et al., 2009). The patients tolerated the active treatments well, adverse side effects were encountered relatively rarely; dry mouth, drowsiness and sedation was 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) (Cutler et al, 2009). ECG alterations (including increased QT interval) were not observed in any patients. Beyond the well-known antipsychotic and antimanic effect of quetiapine (Tandon, 2004; Bowden et al., 2005; Fountoulakis and Vieta, 2008) 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. Furthermore, several open label clinical studies found quetiapine augmentation effective in therapy resistant depression (Sagud et al., 2006; Dorée et al., 2007). In another recent, open-label, naturalistic study 50-600 mg quetiapine (mean: 340 mg/day) in addition to antidepressants (eszcitalopram, mirtazapine, sertraline) produced significantly faster improvement and significantly higher remission rates compared to antidepressant monotherapy in unipolar agitated major depression (Dannlowski et al., 2009).

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 (Fawcett et al., 1990; Jick et al., 2004; Simon et al., 2006; McGirr et al., 2007; Rihmer, 2007). 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 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% in case of patients receiving quetiapine, lithium, lamotrigine and valproate monotherapy, respectively (Altamura et al., 2008b).

The antidepressant mechanism of quetiapine is complex and not yet fully understood. 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) (Cutler et al., 2009). Treatment of hypomanic symptoms frequently present in bipolar I and II and unipolar depression also plays a role in the mechanism of action (Rihmer és Akiskal, 2006; Goodwin és Jamison, 2007; Rihmer, 2008).

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