Quetiapine monotherapy for bipolar depression

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Abstract: Bipolar depression is more common, disabling, and difficult-to-treat than the manic and hypomanic phases that define bipolar disorder. Unlike the treatment of so-called "unipolar" depressions, antidepressants generally are not indicated as monotherapies for bipolar depressions and recent studies suggest that -even when used in combination with traditional mood stabilizers – antidepressants may have questionable value for bipolar depression. The current practice is that mood stabilizers are initiated first as monotherapies; however, the antidepressant efficacy of lithium and valproate is modest at best. Within this context the role of atypical antipsychotics is being evaluated. The combination of olanzapine and the antidepressant fluoxetine was the first treatment to receive regulatory approval in the US specifically for bipolar I depression. Quetiapine was the second medication to be approved for this indication, largely as the result of two pivotal trials known by the acronyms of BOLDER (BipOLar DEpRession) I and II. Both studies demonstrated that two doses of quetiapine (300 mg and 600 mg given once daily at bedtime) were significantly more effective than placebo, with no increased risk of patients switching into mania. Pooling the two studies, quetiapine was effective for both bipolar I and bipolar II depressions and for patients with (and without) a history of rapid cycling. The two doses were comparably effective in both studies. Although the efficacy of quetiapine monotherapy has been established, much additional research is necessary. Further studies are needed to more fully investigate dose-response relationships and comparing quetiapine monotherapy to other mood stabilizers (lithium, valproate, and lamotrigine) in bipolar depression, both singly and in combination. Head-to-head studies are needed comparing quetiapine to the olanzapine-fluoxetine combination. Longer-term studies are needed to confirm the persistence of response and to better gauge effects on metabolic profiles across months of therapy. A prospective study of patients specifically seeking treatment for rapid cycling and those with a history of treatment-emergent affective shifts also is needed. Despite the caveats, as treatment guidelines are revised to incorporate new data, the efficacy and tolerability of quetiapine monotherapy must be given serious consideration.

Keywords: bipolar disorder, manic depression, depression, quetiapine, mood stabilizer

Introduction

Bipolar disorder is a highly recurrent and not infrequently chronic illness that is recognized as one of the world's 10 greatest public health problems (Murray and Lopez 1997). For the majority of patients, the periods of depression far exceed those of mania, in terms of both frequency and duration (Post et al 2003; Judd et al 2002, 2003). For individuals with bipolar I disorder, for example, days spent with depressive symptoms are about three times more common than days spent with hypomanic or manic symptoms (Judd et al 2002). The dominance of the depressed pole of the illness is even more dramatic individuals with bipolar II disorder: in one prospective study conducted across nearly 13 years, patients with bipolar II disorder spent almost 40 times the days with depressive symptoms as compared to the days spent with hypomanic symptoms (Judd et al 2003).

Despite the dramatic and life-disrupting nature of mania, recent studies have also documented that it is the more long-lasting depressive episodes that have the greater

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deleterious effects on quality of life and functionality (Judd et al 2005; Depp et al 2006). The burden imposed by bipolar depression on the family and loved ones exceeds that of bipolar mania or unipolar depression, perhaps all the more remarkable in view of the greater risk of psychosis, violent behaviour, and increased frequency of hospitalization associated with mania (Post 2005; Hirschfeld 2004). The perceived stigma of the condition may also add to the burden placed on the family or primary caregiver (Perlick et al 2004). The assessment of caregiver burden is further impeded by the unique characteristics of bipolar depression – including the unfortunate tendency for milder episodes to go unrecognized or untreated and the high incidence of subsyndromal inter-episode symptoms (Ogilvie et al 2005). Perhaps not surprisingly, the depressive episodes also are more directly linked to reduced longevity in bipolar disorder, particularly through suicide but perhaps also to increased risks of obesity and cardiovascular disease (Dilsaver et al 1997; Fagiolini et al 2002; Mitchell and Malhi 2004).

Despite the obvious clinical importance of the depressed phase of bipolar disorder, remarkably few controlled studies of first- and second-line treatments have been performed (Thase 2005). The paucity of well-designed studies essentially precludes the practice of evidence-based medicine and for some important questions (eg, "If an antidepressant is used and appears to be effective, how long should it be maintained?") there is not consensus about best practices, which no doubt hampers clinical decision-making (Thase 2005; Ostacher 2006). Indeed, in the largest placebo-controlled study of the role of antidepressants in bipolar depression conducted to date, the addition of paroxetine or bupropion to optimized therapy with mood stabilizers resulted in no added benefit as compared to therapy with mood stabilizers alone (Sachs et al 2007). For the prescribing physician, the need to swiftly deliver effective pharmacotherapy to lessen suffering and minimize functional impairments is paramount, and appears to foster the continued use of antidepressants in bipolar depression despite the lack of clear-cut evidence that they improve outcomes. Nevertheless, the decision to initiate therapy with an antidepressant to hasten recovery is not without attendant risks, including treatment-emergent affective switches (TEAS) or acceleration of cycling and, as a result, the ranking of antidepressants in contemporary practice guidelines continues to drop in favor of other strategies (Thase 2005; Yatham et al 2006).

Many expert panels recommend initiating mood stabilizers alone, ie, before considering whether or not an antidepressant is indicated. If one accepts the validity of the "mood stabilizer first" strategy, then lithium and three anticonvulsants (valproate, carbamazepine, and lamotrigine) might be nominated as candidates for first line of therapy for bipolar depression (Thase 2005; Grunze 2005). However, none of these medications is renowned for having powerful antidepressant effects (Thase 2005) and – primarily for reasons of tolerability and safety – few clinicians would use carbamazepine as the first step in a treatment algorithm. Even lithium salts, which arguably have the best evidence of efficacy from placebo-controlled studies (Zornberg and Pope 1993; Thase and Sachs 2000), do not exert particularly robust antidepressant effects (Thase 2005). The search for an effective monotherapy for bipolar depression thus goes on.

Emerging data suggest that the list of medications that are classified as mood stabilizers eventually may need to be expanded to include the class of medications known as atypical antipsychotics. All five of the more widely prescribed atypical antipsychotics (in alphabetical order: aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone) have established antimanic efficacy. Consistent with proposed criteria to define mood stabilizers (see, for example, Ketter and Calabrese 2002; Goodwin and Malhi 2007), atypical antipsychotics are unlikely to cause TEAS and two members of the class (olanzapine and aripiprazole) have received a formal indication for prophylaxis against manic relapse following successful acute therapy. Starting with observations from studies that included patients with mixed manic states, there is slowly increasing evidence to indicate that atypical antipsychotics also have antidepressant effects (Keck 2005; Nemeroff 2005). In fact, the first treatment to be approved by the United States Food and Drug Administration (FDA) specifically for bipolar depression is the proprietary combination of olanzapine and the selective serotonin reuptake inhibitor (SSRI), fluoxetine. In the pivotal trials that led to that indication, olanzapine monotherapy was also studied and found to have intermediate efficacy: greater than placebo but significantly less than the olanzapine-fluoxetine combination (OFC) (Tohen et al 2003).

This review will focus on the second atypical antipsychotic to be systematically studied as a monotherapy for bipolar depression, quetiapine. The results of the research program that led to the FDA approval of quetiapine monotherapy for bipolar depression will be summarized in detail. Quetiapine, which is the first – and currently only – monotherapy approved by the FDA to treat both the depressive and manic episodes associated with bipolar disorder, has been ranked as a first-line treatment of bipolar depression in the recently

updated treatment guidelines published by the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Yatham et al 2006).

Efficacy against depressive symptoms

Regulatory approval of quetiapine monotherapy for bipolar depression was primarily based on two similar randomized controlled trials (RCTs) known by the acronyms BOLDER (BipOLar DEpRession) I and II. Both of these 8-week, placebo-controlled, double-blind studies compared two doses of quetiapine – 300 mg per day and 600 mg per day. Both studies used once daily dosing (at bedtime) and the same rapid titration schedule, with maximum study dose achieved by the 8th day of treatment. Both studies included patients with bipolar I and bipolar II depressive episodes and allowed otherwise eligible patients with histories of rapid cycling to enroll. Both studies used change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score as the primary endpoint. Together, the BOLDER I (Calabrese et al 2005) and BOLDER II (Thase et al 2006) studies represent the largest placebo-controlled data set to date that includes patients with bipolar I and bipolar II depressions.

BOLDER I enrolled 542 patients meeting DSM-IV criteria for a current episode of bipolar I or bipolar II depression, according to DSM-IV criteria (Calabrese et al 2005). In order to enter the study, outpatients had to score at least 20 on the 17-item Hamilton Depression Scale (HAM-D17), as well as have a score of at least 2 on HAM-D item 1 (depressed mood). Pretreatment MADRS scores indicated that the unmedicated study group presented with moderate-to-severe levels of depressive symptoms (see, for example, Muller et al 2003).

Both doses of quetiapine resulted in significant improvements in MADRS total scores at all time points measured, with statistical significance over placebo detected after only 1 week of treatment (the first assessment point of the study) and maintained at every time point thereafter (see Figure 1a). The proportion of patients classified as responders to treatment, defined as a ≥50% improvement in MADRS total score at study endpoint (using the "last observation carried forward [LOCF] convention" to estimate the final scores of study dropouts) was significantly higher in both groups receiving active quetiapine (58% in both groups) than in the group randomized to placebo (36%). Remission rates (defined as a final MADRS total score ≤12) followed a similar pattern (53% for both 300 mg and 600 mg quetiapine, 28% for placebo). Individuals treated with either dose of quetiapine were faster to respond to treatment and to achieve remission than those receiving placebo (median time to response was 22 days for both doses of quetiapine versus 36 days for placebo, and median times to remission were 29, 27, and 65 days for 300 mg quetiapine, 600 mg quetiapine, and placebo, respectively).

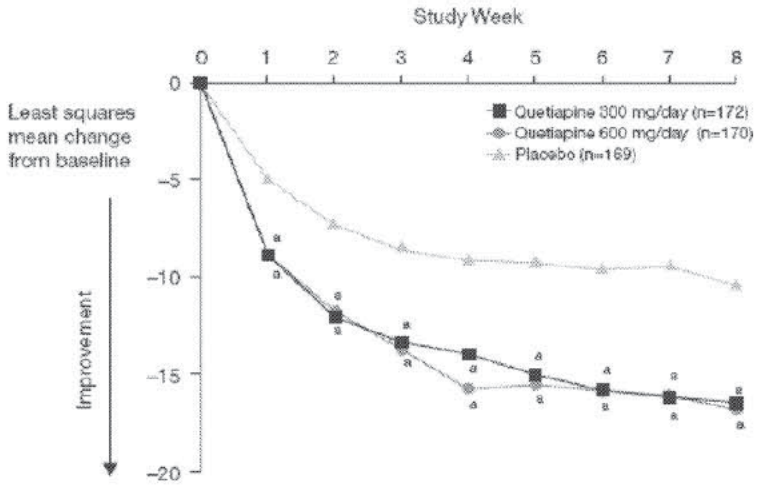
The results of the BOLDER II trial (n = 509) fully replicated the first study in terms of the primary outcome variable, with quetiapine-treated patients displaying significantly greater mean improvement in MADRS total scores than placebo-treated patients at all time points from Week 1 onward (Figure 1b) (Thase et al 2006). Response rates for both doses of quetiapine monotherapy were also similar to those observed in the original study after 8 weeks of treatment (60%, 58%, and 45% for the 300 mg, 600 mg, and placebo groups, respectively), as were remission rates (52% for both groups receiving active quetiapine as compared to 37% for the group receiving placebo). Looking across the two studies, the only appreciable difference was the higher placebo response/remission rates observed in BOLDER II, which could possibly be attributable to increased expectations from physicians and patients alike, in light of the positive findings arising from BOLDER I.

In both BOLDER studies, improvements on the secondary rater-administered measure, the HAM-D_{17}, mirrored those reported on the MADRS scale. For example, both groups receiving active quetiapine again experienced significantly greater mean improvements from Week 1 onward compared with the group receiving placebo.

With respect to the impact of quetiapine on specific depressive symptoms, at study endpoint improvements were detected in nine of the 10 individual items in BOLDER I, and in nine individual items in BOLDER II. Figure 2 summarizes improvements in individual items of the MADRS scale in the BOLDER studies. It is important to note that significant improvements were observed on the core symptoms of depression, including apparent sadness, reported sadness, suicidal thoughts, and pessimistic thoughts, in addition to improvements in sleep and anxiety.

Efficacy in patient subgroups

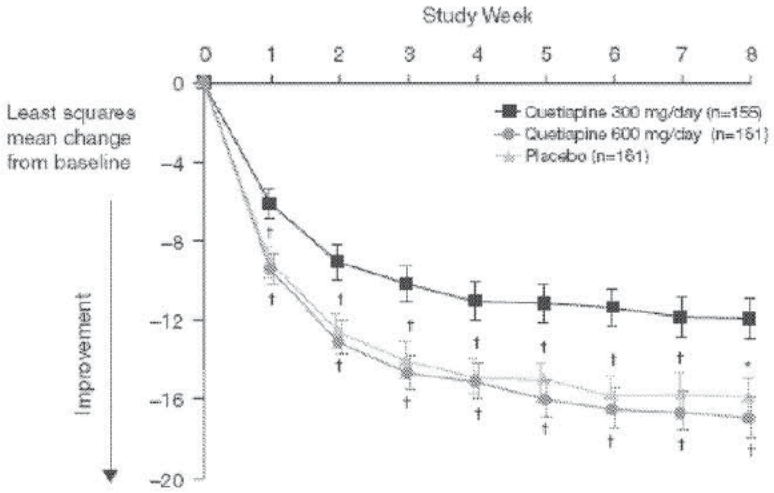
Since the patient populations enrolled in the BOLDER studies included individuals with both bipolar I and bipolar II depression, and those with and without a rapid-cycling disease course, the results of the BOLDER trials were examined to determine if quetiapine was particularly effective – or ineffective – in various patient subgroups. Although there are important differences between bipolar I and bipolar II disorders (as well as between patients who meet criteria for



[a]p<0.001 vs placebo

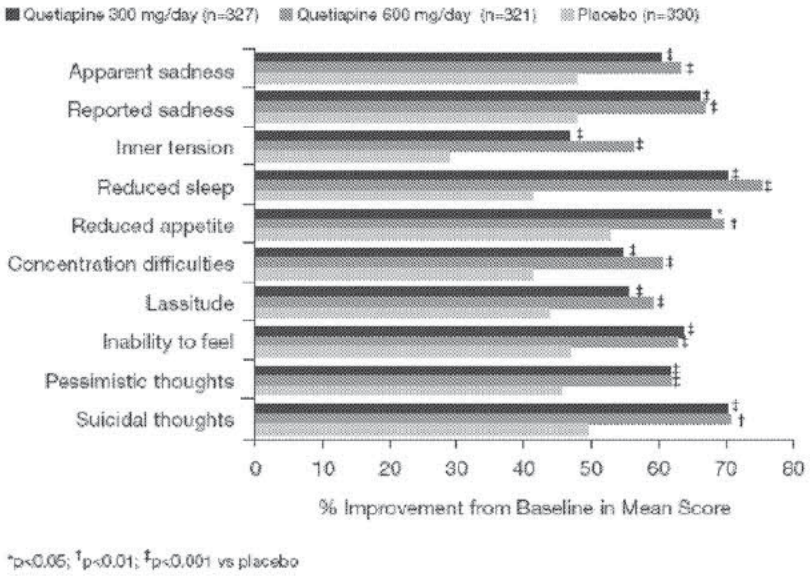
Figure 1a Least-squares mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at each assessment of outpatients with bipolar I or II disorder who experienced a major depressive episode (BOLDER I).

rapid cycling and those who do not) (Yatham et al 2005), demonstration that a novel treatment is comparably effective across the subgroups could greatly simplify clinical management. The combined BOLDER data set shows that both bipolar I and bipolar II patient groups exhibited significant improvements in MADRS total score following treatment with either dose of quetiapine (300 mg per day or 600 mg per day) compared with placebo (Figure 3).



*p<0.01, †p<0.001 vs placebo

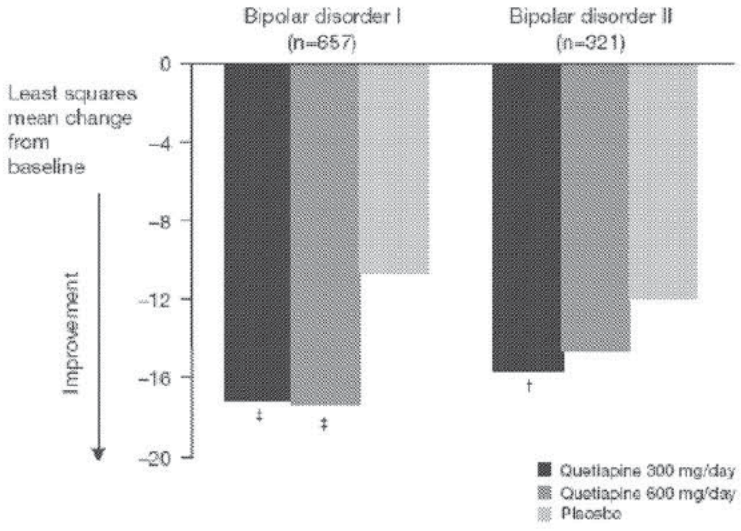
Figure 1b Least-squares mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at each assessment of outpatients with bipolar I or II disorder who experienced a major depressive episode (BOLDER II).



*p<0.05; †p<0.01; ‡p<0.001 vs placebo

Figure 2 Percentage improvement from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) individual items scores in outpatients with bipolar I or II disorder (data pooled from BOLDER I and BOLDER II studies: ITT, LOCF).

Rapid cycling is associated with a poorer treatment response and long-term prognosis, and is associated with greater disability and a higher incidence of suicidal behavior (Schneck 2006). Currently available antidepressants may increase the risk of rapid cycling, and this uncertainty has limited their widespread use (Goldberg and Truman 2003). Results of a subanalysis of BOLDER I indicated that quetiapine was as effective in patients with a history of rapid cycling as among with less frequent episodes (Vieta et al 2007). A not yet published analysis of the combined data from the



†p<0.01; ‡p<0.001 vs placebo
(n at baseline)

Figure 3 Least mean squares change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score in outpatients with bipolar I or II disorder (data pooled from BOLDER I and BOLDER II studies: ITT, LOCF).

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