

# Add-on Quetiapine for Difficult to Treat Bipolar Depression

Naren P. Rao, Ganesan Venkatasubramanian, and Bangalore N. Gangadhar

Department of Psychiatry, National Institute of Mental Health & Neurosciences,  
Bangalore, India

Corresponding author: Dr. G. Venkatasubramanian MD, Associate Professor of Psychiatry, The Metabolic  
Clinic in Psychiatry National Institute of Mental Health & Neurosciences, Hosur Road,  
Bangalore – 560029, India, E-Mail: [venkat.nimhans@yahoo.com](mailto:venkat.nimhans@yahoo.com)

## Abstract

**Background:** “Difficult to treat depression” includes depression that inherently does not respond satisfactorily to one or more treatments that are optimally delivered. Quetiapine is effective for treatment for bipolar depression but its use in “difficult to treat bipolar depression” is yet to be explored.

**Objectives:** To evaluate the effectiveness of quetiapine in “difficult to treat bipolar depression”, as add on agent with mood stabilizers.

**Methods:** Seven patients who had “difficult to treat depression” were treated with add on quetiapine to usual treatment and response to treatment was assessed.

**Results:** Depression improved in all patients after add on quetiapine and maintained improvement for an average duration of follow-up of eleven months. Quetiapine was generally well tolerated without any significant side effects.

**Conclusions:** The addition of quetiapine to usual treatment improves difficult to treat depression in bipolar disorder and is generally safe and well tolerated (*German J Psychiatry* 2010; 13: 41-44).

**Keywords:** quetiapine, difficult to treat depression, depression, bipolar affective disorder, antipsychotic

Received: 1.2.2009

Revised version: 12.3.2010

Published: 17.3.2010

## Introduction

Bipolar disorder is associated with significant burden and is the sixth leading worldwide cause of disability (Woods 2000). There are many effective treatments for the manic phase of the disorder, but treating bipolar depression has proven difficult. This is of great clinical relevance as depression is usually the first and most frequent type of episode in bipolar disorder and on an average people with bipolar disorder spend about three times as much time depressed as manic (Post et al. 2003). “Difficult to treat depression” includes depression that inherently does not respond satisfactorily to one or more treatments that are optimally delivered and also depression treated under circumstances precluding the optimal delivery of potentially effective treatments (Rush et al. 2003). Difficult to treat depression is a useful clinical entity close to real life practice as it includes not only treatment resistant depression (depression which does not respond to optimally delivered treatments) but also

depression resistant due to non adherence, comorbid general medical conditions or substances abuse which could interfere with the efficacy of antidepressant, abnormal absorption, abnormal metabolism. It also encompasses intolerable side effects preventing adequate dose or duration of treatment and resulting in non adherence, comorbid axis II issues that reduce likelihood of remission (Rush et al. 2003).

Recent evidence suggest atypical antipsychotics are effective in treating both phases of bipolar disorder and as effective as established drug therapies (Derry et al. 2007). Quetiapine is efficacious in the treatment of acute bipolar mania (Sachs et al. 2004, Vieta et al. 2007) and is effective in treatment of depressive symptoms in a variety of psychiatric disorders (Calabrese et al. 2005, Derry et al. 2007, Goldberg et al. 2007, Milev et al. 2006, Sajatovic et al. 2001, Sajatovic et al. 2002, Vieta et al. 2007). Recently it has been shown to be effective as adjunctive for treatment of psychotic depression and treatment resistant depression (Wijkstra et al. 2010, Anderson et al. 2009).

**Table 1. Details of medications during study and dosage of add on quetiapine**

Case No	Sex	Age	Treatment during study	Add-on quetiapine
1	F	42	Valproate 1500 mg	600 mg
2	M	50	Valproate 1250 mg, sertraline 200mg	200 mg
3	M	24	Valproate 1000mg, Chlorpromazine 300mg	400 mg
4	M	19	Valproate 800mg	200 mg
5	M	63	Lithium 800mg, risperidone 4mg	400mg
6	F	62	Lithium 900mg, escitalopram 20 mg	400 mg
7	M	19	Lamotrigine 200mg, aripiprazole 20 mg	300mg

It has been approved for treatment for bipolar depression by FDA. But use of quetiapine in “difficult to treat bipolar depression” is less explored (Milev et al. 2006). A Pubmed (MeSH database) search with key words as “difficult to treat depression AND quetiapine” did not reveal relevant papers. In this report we present first time use of quetiapine as add on agent in “difficult to treat” bipolar depression.

## Method

Seven patients attending the clinical service of National Institute of Mental Health And Neuro Sciences (NIMHANS), Bangalore, India who had “difficult to treat” depression were studied. Quetiapine was used as add-on agent to existing treatment (Table 1). Bipolar disorder was defined on ICD-10 criteria and “difficult to treat depression” was defined as described above (Rush et al. 2003). Clinical response after the start of quetiapine treatment was determined from reports by patients, relatives and clinical interview.

## Results

All seven patients included in the series had persistent symptoms of depression despite treatment with mood stabilizer and thus satisfied criteria for “difficult to treat depression”. Four patients were on treatment with valproate, two with lithium and one with lamotrigine. Two patients had a switch to mania when given a trial of antidepressant earlier. Quetiapine was started as add on agent in these patients, to the existing mood stabilizer. Depressive symptoms improved in all patients as perceived by the treating clinician, patient and the caregivers. Depressed mood and sleep were the main dimensions of improvement. Quetiapine was generally safe, well tolerated and all patients remained on quetiapine at the end of average observation period of eleven months. None

of the patients had a switch to mania or hypomania and no clinically significant adverse events (related to increased prolactin, tardive dyskinesia, weight gain) were observed.

## Case Reports

### Case 1

Mrs. C, 42 year old female from an urban background, presented with history of multiple manic and depressive episodes for the past 28 years with each episode lasting for 2-3 months. She had rapid cycling pattern for last 2 years. She earlier had a switch to mania with bupropion and Electroconvulsive therapy (ECT). She presented with a two week history of pervasive sad mood, fatigability, anhedonia, decreased interaction and decreased sleep while on treatment with valproate 1500 mg per day. Her Physical examination was normal and mental status examination showed decreased speech output, psychomotor retardation, depressive cognition, extreme tearfulness. Her thyroid function, hemogram, liver and renal functions were normal. Patient was diagnosed as bipolar affective disorder, currently severe depression without psychotic symptoms and quetiapine was added and increased to 600 mg. Patient showed improvement in the next 4 weeks and symptoms remitted. Improvement was maintained and had no episodes for the next one year.

### Case 2

Mr. P, 50 year old married male with more than 10 manic and depressive episodes in the past and history of ischemic heart disease with hypertension presented with complaints of dullness, morning worsening of sad mood, slowness in work, disturbed sleep when he was on valproate 1250 mg. Mental status examination showed psychomotor retardation, decreased speech, increased reaction time, depressed affect. Earlier he was treated with sertraline 200mg along with valproate and carbamazepine without improvement in symptoms. Patient was started on quetiapine 200 mg along with valproate, and reported significant improvement especially in mood symptoms and disturbed sleep. The patient was maintaining well without further depressive episode for the next 18 months.

### Case 3

Mr. S, 24 year old unmarried male with past history of trigeminal neuralgia, 2 episodes of mania in the past 2 years presented with sad mood, decreased interaction with others, delusion of persecution and reference, decreased sleep and appetite. He was on 1000mg of valproate and chlorpromazine 300mg per day. Patient was started quetiapine and increased to 400mg per day and chlorpromazine was stopped. In a month there was improvement in depressed mood and

there were no delusions. His sleep was normal to pre-morbid level. He was maintaining euthymic after 15 months.

#### Case 4

Mr. D, 19 year old unmarried male with history of one episode of mania in the past presented with depressed mood, anhedonia, psychomotor retardation and disturbed sleep and decreased appetite. Patient was on treatment with valproate 800 mg per day. Patient was later started on Quetiapine 200 mg per day. After 3 weeks he reported subjective improvement and there was no psychomotor retardation objectively. He had no further episodes in the next 15 months.

#### Case 5

Mr. R, 63 year old male with past history of two episodes of mania, one episode of hypomania and one depressive episode presented with one and half year duration of illness characterized by pervasive sadness, anhedonia, easy fatigability, ideas of worthlessness, decreased speech, irritability, disturbed sleep and appetite. He was on treatment with Lithium 800 mg, Risperidone 4mg with no improvement in symptoms. He was started on Quetiapine 100 mg per day and gradually increased to 400 mg per day. Risperidone was stopped. Patient reported improvement in mood symptoms after 6 weeks. His sleep was normal and reached pre-morbid level of functioning.

#### Case 6

Mrs. R, 62 year old female with history of angle closure glaucoma, 15 episodes of depression, one episode of mania in the past presented with 6 months duration of depressive symptoms. She was on lithium 600 mg. Lithium was increased to 900 mg and escitalopram 20 mg was started. Patient continued to have depressive symptoms after 4 weeks. Quetiapine 200 mg was started and increased to 400 mg after 2 weeks and escitalopram was stopped. Patient showed minimal improvement in her mood symptoms after 2 weeks and significant improvement was noted after 4 weeks. She did not have further depressive episode in the next 8 months.

#### Case 7

Mr.S, 19 year old male with past history of one episode of hypomanic episode, one episode of depression and drug induced switch with escitalopram presented with 2 months duration of illness characterized by pervasive sad mood, anhedonia, easy fatigability, lack of attention, concentration, low self esteem, death wishes, lack of reactivity, suicidal attempts, increased appetite, weight gain, terminal insomnia. Evaluation of pre-morbid personality showed anxious avoidant personality disorder. He was on treatment with lamotrigine 200mg and aripiprazole 20mg. Quetiapine was started

and increased to 300mg with which he improved in his symptoms in 4 weeks. There was significant improvement in insomnia, sad mood. There were no suicidal ideas and attempts. He was able to function at pre-morbid level. He was maintaining improvement for the next 12 months.

## Discussion

To the best of our knowledge this is the first report of use of quetiapine in difficult to treat depression. Though mood stabilizers and antidepressants have been the standard care for bipolar depression, the treatment of bipolar depression is still an unmet clinical need (Yatham et al. 2003). Of all the mood stabilizers only lithium and lamotrigine have specific antidepressant effect, but response of bipolar depression to lithium is often incomplete in a substantial proportion of patients (Zornberg et al. 1993) and efficacy of lamotrigine in treatment of acute bipolar depression has been demonstrated in only a few trials (Calabrese et al. 1999). Use of antidepressants alone increases the risk of a switch to mania or hypomania and standard antidepressant medication, as compared with the use of mood stabilizers, is not associated with increased efficacy (Sachs et al. 2007). Therefore, there is a need for new therapies that provide a rapid onset of antidepressant efficacy, improved tolerability, and low risk of treatment emergent mania or cycle acceleration (Cookson et al. 2007).

Atypical antipsychotic agents have efficacy in treatment of bipolar mania and depression, though the mechanism of their action is not clear. Dopamine receptor blockade and serotonin receptor blockade have been postulated for anti-manic and antidepressant effects respectively (Vieta 2005). Olanzapine in combination with fluoxetine is efficacious in treatment of bipolar depression (Tohen et al. 2003). As discussed in introduction, Quetiapine has also been shown to be efficacious in treatment of bipolar depression and rapid cycling bipolar disorder, but it has not been well studied for treatment of "difficult to treat" depression.

The current report provides preliminary evidence that quetiapine is effective in treatment of difficult to treat depression, who do not respond completely to established mood stabilizers. Quetiapine was well tolerated in all patients without any significant side-effects. Notably, none of the patients had switch to mania or hypomania though two patients had earlier switch with antidepressant. Current findings are consistent with another open label trial of quetiapine as add on agent, in which there was a 55% mean reduction of Hamilton depression rating scale scores (Milev et al. 2006). Also, major improvements were noted in depressed mood and insomnia similar to current findings. Thus the findings demonstrates the benefits of quetiapine as a possible therapy for difficult to treat bipolar depression. Quetiapine's side effect profile and tolerability are also important factors in its consideration for treatment.

The findings of the study are limited by the small number of patients and absence of objective measures of depression. All evaluation of changes in behavior and affect were based on subjective and clinical impressions. The generalizability of

these findings must be determined through randomized controlled studies with larger numbers of patients.

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