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Role of Amisulpride Augmentation in Treatment Resistant Major Depressive Disorder: An Open Label Study from North India

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ABSTRACT: ***Background:*** *About 60% patients with major depressive disorder do not achieve a sufficient response to standard antidepressant therapy and about two-thirds of patients receiving initial antidepressant medication do not achieve remission. Various strategies are being employed to counter this problem. Studies have shown that atypical antipsychotics, augmented to antidepressants for major depressive disorder patients, produced higher response and remission rates. The data regarding the augmentation of antidepressants with amisulpride is very scarce as compared to other atypical antipsychotics.* ***Objective:*** *To evaluate whether augmentation with amisulpride is effective and tolerable in patients of major depressive disorder (MDD) who did not respond significantly to adequate trials of standard antidepressants.* ***Methodology and Results:*** *In our open label 6 weeks study, amisulpride was added to baseline antidepressant medication of treatment resistant patients of major depressive disorder. A total of 112 patients enrolled in the study with a mean age of 39.37 years out of which 83% completed the study. Over a period of 6 weeks, 71% patient showed response and 40% patient remitted ($p<0.001$) with a mean amisulpride dose of 135.31 mg/day. The mean decrease in HAM-D17 score was 16.17 points. There was more than 2 point change in mean CGI-S score from base line to endpoint. Common adverse effects were akathisia (4.64%), sleep disturbances (10.71%), restlessness (5.36%) and extrapyramydial side-effects (4.64%).* ***Conclusion:*** *Augmentation of antidepressant drugs with low doses of amisulpride seems to be effective and tolerable in patients of major depressive disorder who do not respond adequately to standard antidepressant medications.*

Key words: *Amisulpride, augmentation, treatment resistant major depressive disorder, atypical antipsychotics*

INTRODUCTION

Treatment resistant depression is a complex spectrum of severity rather than a single uniform entity and is difficult to treat successfully and outcomes are inadequate (Dunner et al., 2006; Trivedi et al., 2004). Approximately 60% patients with MDD do not achieve a sufficient response and about two-thirds of patients receiving initial antidepressant therapy do not achieve timely remission (John Rush et al., 2006; Fava et al., 2003). The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) treatment, the gold standard trial showed an average response rate of 47% and remission rates of around 30% for patients treated in 23 psychiatric and 18 primary care settings (Trivedi et al., 2006). Thase and Rush have proposed a multi-staging system based on prior treatment response which divides treatment resistant depression into 5 stages. Stage 1 = non response to adequate trial of one antidepressants, stage 2 = non response to adequate trial of two antidepressants with different pharmacological profiles, stage 3 = stage 2 plus failure of one augmentation strategy, stage4 = stage three plus failure of two augmentation strategies, stage 5 = stage 4 plus failure to respond to electroconvulsive therapy (ECT) (Thase & Rush, 1997).

The main strategies to deal with the problem of treatment resistant depression include optimizing existing treatment, switching medications, augmentation, combining antidepressants, adding psychotherapy, and finally, ECT. Evidence regarding pharmacotherapy and psychotherapy especially cognitive behavior therapy (CBT) has been enhanced by results from the STAR*D (Rush et al., 2006). Though, there is limited evidence or data to support one optimal treatment strategy over another for treatment resistant depression, augmentation strategies have potential advantages of rapid response and minimal loss of time between regimens, maintenance of any partial response to the initial treatment and they also provide the clinician an opportunity to influence several neuromodulators or neurotransmitters at the same time which could be therapeutically beneficial (Nelson, 2002). Augmentation with atypical antipsychotics is widely used approach for treatment resistant depression and also supported by various treatment guidelines including Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines and several meta-analyses (Lam et al., 2009). Papakostas et al., in a meta-analysis involving a total of 1500 outpatients with treatment-resistant major depressive disorder found a pooled remission rate of 47.4% with adjunctive atypical antipsychotics vs. 22.3% for adjunctive placebo and response rates were 57.2% vs. 35.4% for adjunctive atypical antipsychotics and adjunctive placebo respectively but the rate of discontinuation due to adverse events was higher in antipsychotic group (Papakostas et al., 2007). Another meta-analysis by Nelson et al. to determine the efficacy and tolerability of adjunctive atypical antipsychotic agents (olanzapine, risperidone, quetiapine, aripiprazole) in major depressive disorder found that adjunctive atypical antipsychotic agents are effective augmentation agents in major depressive disorder but are associated with an increased risk of discontinuation due to adverse events (Nelson & Papakostas, 2009). Similar findings were noted in another meta-analysis involving

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olanzapine, quetiapine, aripiprazole, and risperidone by Wen et al. (Wen et al., 2014).

The data regarding the augmentation of antidepressants with amisulpride is very scarce as compared to other atypical antipsychotics though studies have already shown that amisulpride helps in improving depressive symptoms in patients with schizophrenia (Kim et al., 2007). Early studies in patients with dysthymia (Ravizza, 1999; Smeraldi, 1998; Lecrubier et al., 1997; Boyer et al., 1998) that compared Amisulpride with fluoxetine, imipramine, and amitriptyline support the clinical observation that amisulpride may have antidepressant activity and efficacy similar to antidepressants (Papp & Wieronska, 2000). Amisulpride has high affinity for the dopamine D2/D3 receptors more so for D3 than D2 and has little or no affinity for D1, D4, D5, serotonin, alpha-adrenergic, H1 histaminergic or anticholinergic receptors (Scatton et al., 1997; Barclay, 2002). At low doses, Amisulpride enhances dopamine transmission by selectively binding to presynaptic autoreceptors (Guyon et al., 1993). It is hypothesized that there is decreased dopaminergic neurotransmission in aspects of mood disorders such as anhedonia and psychomotor slowing. This might explain amisulpride action as antidepressant at low doses (Dunlop et al., 2007).

Amisulpride has been frequently used in Kashmir, India as an add-on drug in patients who do not respond adequately to antidepressants. There has been no study about role of amisulpride as an augmentation agent in depression from this part of the world. To address this issue this following study was carried out. The aim of this study was (1) to evaluate whether the augmentation with amisulpride is helpful in patients with MDD who did not respond significantly to adequate trial of standard antidepressants medications, and (2) to assess the tolerability of amisulpride when added to antidepressant medications as an adjunctive medication in patients of major depressive disorder.

METHODOLOGY

This study was a prospective, 6 week, open label study to assess the clinical benefit and safety of amisulpride as an augmenting agent to antidepressant medications in patients with major depressive disorder who did not benefit adequately from standard antidepressant medications. This study was conducted from June 2013 through November 2014 after seeking permission from the departmental ethical committee.

Patients both males and females aged between 18 to 65 years attending outpatient unit of Government Psychiatric Diseases Hospital, Srinagar, Kashmir, India who were diagnosed as Major Depressive Disorder using DSM-IV TR criterion and were considered as treatment resistant. Treatment resistance was operationally defined in our study as those patients who met DSM-IV TR criteria for Major Depressive Disorder (MDD) without psychotic features, had a baseline HAM-D 17 score of ≥18, previously had a failure to respond (<50% reduction in baseline HAM-D 17 score) to adequate trials of at least two antidepressants from two different classes lasting ≥6 weeks each at an adequate dosage (Hamilton, 1960). Adequate dosages were taken as daily dosages of more than or equal to 20 mgs of escitalopram, 60 mgs of fluoxetine, 37.5 mgs of paroxetine, 150 mgs of sertraline, 200 mgs of fluvoxamine, 45 mgs of mirtazepine, 225 mgs of venlafaxine XR, 60 mgs of duloxetine, 300 mgs of bupropion XR, 150 mgs of nortriptiline, 150 mgs of amitriptyline or imipramine, 225 mgs of dosulepin.

Exclusion criteria were diagnosis of Bipolar Affective Disorder, Schizophrenia or other Psychotic Disorders, active suicidal ideations or recent suicidal attempt, any current substance related disorder, co-morbid Obsessive Compulsive Disorder, any history of hypersensitivity to amisulpride, any serious medical disorder and pregnancy and if the patient had received an adjunctive antipsychotic in the last 4 weeks duration. Patients taking concurrent benzodiazepines, sedative hypnotics medications were not excluded. Written informed consent was obtained from all the patients who were included in study. Patient's clinical history was reviewed and urine drug and pregnancy screen, routine investigations including complete blood counts, liver function tests, renal function tests, thyroid status, electrolytes, prolactin levels and ECG were done before starting amisulpride.

Amisulpride was added to baseline medication at a dose of 50 mgs. Depending on the clinical response and tolerability, amisulpride was increased at a weekly increment of 25 mgs up to a maximum of 200 mgs. The dosage of baseline antidepressant medications remained unchanged unless patients complained of any intolerable antidepressant related side effects. HAM-D 17 and CGI-S scales were applied at baseline and each visit while and CGI-I were applied at week 2, 4 and 6. (Hamilton, 1960; Guy, 1976a) Response was defined as ≥50% reduction in HAM-D 17 score from beginning to end of treatment. Remission was defined as HAM-D 17 score of ≤7 at endpoint. Clinical safety was assessed by spontaneous notification of adverse events, measurement of vital signs, body weight and by laboratory parameters and ECG. Extra-pyramidal side effects were evaluated using the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale and Barnes Akathisia Clinical Assessment (BARS) (Simpson et al., 1970; Guy, 1976b; Barnes, 1989).

Data was analyzed using the SPSS 17 software. Last Observation Carried Forward (LOCF) has been employed for data imputation. Continuous variables were summarized as mean and standard deviation. Categorical variables were summarized as percentages. Repeated measures analysis of variance (rANOVA) was used to analyze the difference in the values of a continuous variable through time. Friedman test was applied for ordinal variables (CGI-I and CGI-S). Chocrane's Q test was used for comparing remission and response rates. Statistical significance was set at $p<0.05$.

RESULTS

During the study period a total of 112 patients were recruited. Table 1 summarizes the general patient characteristics.

83.92% (94) patients completed study while 18 were drop outs. 6(5.36%) patients discontinued due to adverse effects, 7(6.25%) were lost to follow up, 3(2.68%) patients left because of lack of efficacy while 2(1.78%) patients became non compliant during the study. 4 patients dropped due to galactorrhea, 1 of the subjects dropped due to severe akathisia while 1 patient stopped the drug due to insomnia. Table 2 describes the treatment emergent side effects.

The changes in HAM-D 17, CGI-I and CGI-S scores are summarized in Table 3. The change in mean HAM-D 17 scores from baseline to week 6 was 16.17 and results were highly significant ($p<0.001$) (r ANOVA). Change in mean CGI-S scores from baseline to week 6 was 2.20.

50 patients i.e. 44.64% responded at week 4 which increased to 80 i.e. 71.42% at week 6. Treatment response was defined as ≥50% reduction in HAM-D 17 score from beginning to end of treatment. Results were highly significant ($p<0.001$) (Cochran's Q test). 5 patients i.e. 4.46% were in remission at week 4 which increased to 45 i.e. 40.18% at week 6. Remission was defined as HAM-D 17 score of ≤7 at endpoint. Results were highly significant ($p<0.001$) (Table 4).

55.36% (62) patients were on a single antidepressant at the time of augmentation with amisulpride while 44.64% (50) patients were on two antidepressants. Out of 62 patients who were on single antidepressants 31.25% (35) were on a serotonin nor epinephrine

Table 1.
General Characteristics of Patients (N = 112)

Mean Age *(S.D.)*	39.37 years (10.83)
Sex Males Females	 45(40.17%) 67(59.83%)
Marital status Married Unmarried Divorced	 84(75.0%) 19(16.96%) 09(8.04%)
Family type Nuclear Joint	 31(27.68%) 81(72.32%)
Employment status Employed Unemployed	 47(41.96%) 65(58.04%)
Residence Urban Rural	 33(29.47%) 79(70.53%)
Education in years *(S.D.)*	10.71(2.74)
WEIGHT mean (S.D.)	68.43 Kg (12.23)
Mean Duration of illness *(S.D.)*	8.01 years (5.36)
Mean No. of depressive episodes *(S.D.)*	3.65 (2.17)
Mean Duration of current episode *(S.D.)*	11.22 months (3.52)
Mean dose of amisulpride	135.31 mgs
Mean HAM-D baseline score (S.D.)	24.09 (2.30)
No. of previous adequate antidepressant trials in the current episode 2 3	 60 (53.57%) 52(46.43%)

Table 2.
Treatment Emergent Adverse Effects

Adverse effects	**N (%)**
Akathisia	5(4.64%)
Tremors	4(3.57%)
Dry mouth	9(8.03%)
Sleep disturbances	12(10.71%)
Restlessness	6(5.36%)
Extra Pyramidal Side Effects	5(4.64%)
Galactorrhoea	4(3.57%)

reuptake inhibitors (SNRI's), 13.39% (15) were taking selective serotonin reuptake inhibitors (SSRI's) while only 10.71% (12) were on tricyclic antidepressants (TCA's). Out of those who were on combination of antidepressants, 19.64% (22) were on a combination of SNRI and mirtazepine, 10.71% (12) were on a combination of SSRI and mirtazepine, 9.82% (11) were on a combination of TCA and another antidepressant drug while only 4.46% (5) were on a combination of bupropion and another antidepressant drug. 74.10 % (83) patients were taking non-study drugs like benzodiazepines, other sedative hypnotics and beta-blocker at some point of time during the study.

DISCUSSION

This is the first study of its kind from Kashmir examining the role of amisulpride in treatment resistant depression. Our results showed that amisulpride is effective as an augmentation agent in patients of major depressive disorder who fail to respond adequately to standard antidepressant drugs. 83.92% patients completed study while 16.07% were drop outs which were fairly low. The results of our study support the use of adjuvant amisulpride in treatment resistant depression as 71% patients showed response while 40% patients were in remission at week 6. There was a 16 point change in mean HAM-D 17 scores from baseline to 6 weeks while about 2 point change in mean CGI-I score from week 2 to week 6. The response rate in our study is similar to study by Smeraldi who compared amisulpride with fluoxetine in dysthymia and single episode of Major depression patients in partial remission and found a response rate of 74% in patients on amisulpride as monotherapy while in a study by Boyer et al., who compared amisulpride with amineptine and placebo in patients with dysthymia over a period of 3 months confirmed the efficacy of amisulpride as monotherapy in patients with dysthymia with response rates of 63% in amisulpride group as compared to 33% in placebo group (Smeraldi, 1998; Boyer et al., 1998). Moreover our findings are consistent with the remission and response rates showed by other atypical antipsychotics used for antidepressants augmentation. In a study by Patkar et al. 70% of the patients responded while 30% of the patients had remission with aripiprazole as an augmenting agent (Patkar et al., 2006). While in a study by Alexopoulos et al. 68% patient met the criterion for remission with risperidone augmentation of citalopram (Alexopoulos et al., 2008). Corya et al. in a long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination found a response rate of 62% and a remission rate of 56% (Corya et al., 2003). Whereas Papakostas et al. in a study of Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder found a response rate of 61.5% and a remission rate of 38.5% (Papakostas et al., 2004). Though Nelson et al. in a meta-analysis of atypical antipsychotics augmentation in MDD patients found an overall pooled response rate for treatment with an atypical agent was 44.2%, compared with 29.9% for placebo (Nelson et al., 2009). The antipsychotic included in meta-analysis were olanzapine, risperidone, quetiapine and aripiprazole.

A plausible explanation of this beneficial effect could be because of involvement of dopamine in mesolimbic and mesocortical pathways which are involved in reward mechanisms and mood regulation (Javoy-Agid et al., 1980; Braak et al., 2003; Willner, 1983). Dopamine is a neuromodulator which also include neurotransmitters like serotonin, noradrenaline and acetylcholine as well as hormones (e.g. testosterone, oxytocin and vasopressin) (Robbins et al., 2009). Neuromodulators work by binding to different kinds of 'receptors' and the distribution of different receptor types can vary across the brain. The consequence of this neuronal architecture is that neuromodulators, when released, can have different effects in different brain regions according to the type of receptor activated (Crockett & Fehr, 2013). The frontal cortex and the mesolimbic dopaminergic system have high density of D3 receptors; both animal and human studies have suggested a role for D3 receptors in the pathogenesis and treatment of depression (Dikeos et al., 1999; Basso et al., 2005). The dose of amisulpride has important implications in manipulation of dopamine levels (Crockett & Fehr, 2013). At high doses, amisulpride blocks postsynaptic receptors, acting as an antipsychotic, whereas at low doses, it preferentially blocks the presynaptic D2 and D3 autoreceptors, reducing the negative neuronal feedback and inducing an increase of dopamine release (Schoemaker et al., 1997). Therefore, at low dosages, amisulpride acts as a prodopaminergic compound able to reduce the dopaminergic hypoactivity that is often related to depression (Racagni et al., 2003). This mechanism of increasing dopamine transmission might be responsible for the augmentation of antidepressants in patients with treatment resistant depression. However, Abbas et al., in their study on 5-HT7 receptor knockout mice concluded that it is 5-HT7a receptor antagonism which is responsible for antidepressant activity of amisulpride (Abbas et al., 2009).

Another explanation for response to amisulpride augmentation in our patients might be attributed to the possibility of the diagnosis of bipolar spectrum disorder in some of these patients. A naturalistic study by Sharma et al., suggested that the majority of cases of unipolar treatment resistant depression, occurring in the context of loss of antidepressant response, have a bipolar diathesis (Sharma et al., 2005). The mean duration of the illness was more than 8 years while mean number of depressive episodes was close to 4 in our

Table 3.
Mean Change in Scores (SD)

	0 weeks	2 weeks	4 weeks	6 weeks	Significance (P)
HAM D 17 Scores	24.09 (2.30)	17.57(2.85)	12.38(3.36)	7.92(3.11)	<0.001 **(rANOVA)**
CGI-I scores	-	3.37(0.64)	2.18(1.11)	1.49 (0.97)	<0.001 **(Friedman test)**
CGI-S Scores	4.21 (0.65)	-	-	2.01(0.54)	<0.001 **Wilcoxon signed ranks test**

Table 4.
Response and Remission Rates

	2 Weeks	4 Weeks	6 Weeks	P-value*
No. of patients responding at (>50% decrease in HAM-D score from baseline)	0	50	80	<0.001
No of patients remitting at (HAM-D score of ≤ 7)	0	5	45	<0.001

*Cochran's Q test

study. Moreover age of onset was also low as the mean age of our subjects was 39 years at the time of study. Mitchell et al. suggested a probalistic approach in which a person experiencing a major depressive episode with no clear prior episodes of mania, early onset of first depression, multiple prior episodes of depression, and short duration of current episode increases the likelihood of a diagnosis of bipolar depression than unipolar depression(Mitchell et al., 2008). However, the mean duration of current depressive episode was more than 11 months, which won't favor a diagnosis of bipolar spectrum in our study.

Amisulpride unlike other atypical antipsychotics undergoes relatively little metabolism with about 50% of the dose excreted in the urine as unchanged drug. It undergoes N-dealkylation and oxidation, but the isoenzymes involved in these reactions are yet unidentified. Because of its marginal metabolism, concomitant administration of drugs acting as inhibitors or inducers of the enzymes involved in the biotransformation does not interfere its levels, thus minimizing clinically relevant interactions (Rosenzweig et al., 2002).

However amisulpride leads to reversible hyperprolactinemia as a result of dopamine D2 blockade and may cause endocrine symptoms. In our study 4 cases (all females) had galactorrhoea due to which they had to discontinue amisulpride. Two other patients dropped out of study due to side effects like akathisia and insomnia. In majority of the patients side effects either improved over time or responded to addition of benzodiazepines or beta-blockers. No serious adverse effect was noted other than galactorrhoea. None of the subjects had significant weight changes during the study. Menstrual disturbances were not seen as it was only a 6 weeks study.

One of the several limitations of our study was its short duration i.e. 6 weeks thereby preventing us from assessing long term effects of adjunctive amisulpride in depressive patients. Amisulpride augmentation in our study showed high rates of remission and response in 6 weeks, but due to short duration and design of our study we could not determine whether continuation of amisulpride augmentation in the long term in those who remitted would maintain the remission or relapse. This is an important question keeping in mind the fact that long term use of amisulpride could lead to serious adverse effects especially endocrine and metabolic side effects impairing the quality of life of patients. Most of the previous studies of atypical antipsychotic agents as adjunctive agents were of short duration varying from 4 to 12 weeks. But Rappaport et al., in a three phase study involving about 500 patients with 4–6 weeks of open-label citalopram monotherapy, 4–6 weeks of open-label risperidone augmentation, and a 24-week double-blind, placebo-controlled discontinuation phase could not find significant difference between relapse rate in risperidone group and placebo group (Rapaport et al., 2006). Similarly, Alexopoulos et al. in a placebo controlled study of relapse prevention with risperidone augmentation in older patients with resistant depression found no difference in relapse rate in two groups after 24 weeks (Alexopoulos et al., 2008).

Other limitations are lack of a placebo group which didn't allow us to differentiate effects of augmentation with amisulpride from improvement with continuation of antidepressants and limitations inherent to an open label design. Patients taking other non-study drugs like benzodiazepines were not excluded which could be a potential confounding factor. The definition of treatment resistant depression which was taken in our study as stage 2 treatment resistant depression as per Thase and Rush classification could also be the reason for high rates of remission and recovery (Thase & Rush 1997).

CONCLUSION

Our study concludes that the augmentation of antidepressant drugs with low doses of amisulpride seems to be effective and tolerable in patients of major depressive disorder who do not respond adequately to standard antidepressant medications. Due to the limitations of our study, it is necessary to conduct large randomized, double blind, placebo controlled, long term studies to evaluate the efficacy and tolerability of amisulpride augmentation in treatment resistant depression. Genetic, clinical or demographic characteristics of the patient population responding to amisulpride augmentation remain an interesting area of further research.

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