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COMPARATIVE EVALUATION OF EFFICACY AND SAFETY OF ZIPRASIDONE VERSUS QUETIAPINE AUGMENTATION WITH ESCITALOPRAM IN PATIENTS OF MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Many patients of depression suffering from depression do not improve or show a partial response to conventional antidepressant therapy. Augmentation with atypical antipsychotics enhances the antidepressant action and builds on partial remission. This study was carried out to compare ziprasidone & quetiapine augmentation with escitalopram in patients with major depressive disorder (MDD). It was a prospective, open-label, randomized, comparative clinical study. At the end of 6 weeks with escitalopram (20 mg per day), the eligible patients, showing inadequate response to treatment, were randomly allocated to 2 treatment groups; augmented with quetiapine 200 mg once daily or ziprasidone 20 mg twice daily orally for 6 weeks. Key inclusion criteria were adult patients who met criteria for MDD as defined by DSM-5, and with inadequate clinical response to escitalopram 20mg per day for 6 weeks and HAM-D score of 15 or more on 17 item version, at the screening of the study. Key exclusion criteria were depression with psychotic features and bipolar disorder. Efficacy was assessed using Beck's depression inventory (BDI) scores at 2, 4, and 6 weeks. The baseline BDI score was (33.15 ± 0.678) in the quetiapine group and (32.35±0.466) in the ziprasidone group. BDI score was significantly reduced to (11.40 ± 0.320) & (10.65 ± 0.233) at 6 weeks in quetiapine and ziprasidone groups respectively. All the ADRs were of mild Grade, and none of them warranted any discontinuation of treatment, and augmentation of antidepressant therapy with quetiapine and ziprasidone was found to be safe and effective.

KEYWORDS: MDD, DSM-5, BDI, Ziprasidone, Quetiapine, Escitalopram.

INTRODUCTION

At a global level, over 300 million people suffer from depression, equivalent to 4.4% of the world's population. In India, about 57 million people (18% of the global estimate) are affected by depression. As per National Mental Health Survey (2015-16) in India, one in 20 (5.25%) people over 18 years of age have suffered from depression at least once in their lifetime, amounting to a total of over 45 million people suffering from depression in 2015 itself.[1] Despite being an important health issue, many people with depression remain undiagnosed. However, not all patients show remission to antidepressant therapy, and there are about 10% to 30% of patients who respond inadequately to antidepressant treatment. Also, the treatment of depression is complicated, with a high incidence of relapse and recurrence, even in patients who initially remit. Studies have shown that people with residual symptoms have a poorer prognosis, substantially increasing the risk of subsequent relapses and death. To improve quality of life (QOL) in a patient with depression, it becomes imperative to expand our horizons and explore new vistas to better mental health, ensuring a safe and efficacious approach.[2]

Optimal treatment of Major Depressive Disorder (MDD) is a two-pronged approach, which consists of psychotherapy and pharmacotherapy. Psychotherapy alone is generally recommended for mild to moderate types of depression, which includes cognitive therapy, interpersonal psychotherapy, problem-solving therapy, psychodynamic-interpersonal psychotherapy, and psychoanalytically oriented psychotherapy.[3] Patients with severe depression do not respond well to psychotherapy alone and require pharmacological intervention as well. The choice of pharmacotherapy solely depends upon the clinician's point of view, considering the drug's tolerability, safety, and efficacy. The selection of the antidepressant medication is based on the type of symptoms of the patient and the severity of those symptoms. Various groups of antidepressant drugs used are tricyclic and tetracyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs). Herbal medicines like Hypericum perforatum (St. John's wort), amino acid derivative S-adenosylmethionine (SAM-e), tryptophan and 5- hydroxytryptophan (5-HT) dietary supplements are also said to be effective in the management of MDD. SSRIs are the first-line

drugs for depression, whereas MAO inhibitors remain as second- choice drugs. SSRIs and newer antidepressants are better tolerated than TCAs and are safer in overdose.[4]

In patients showing partial response to antidepressant medicines, with the residual symptom, various therapeutic strategies may be tried like, optimization of antidepressants, switching of antidepressant of one class with another SSRI/SNRI with TCA or MAO inhibitors, combining antidepressants from different classes such as SSRI and TCA, TCA and MAOI, etc., and augmentation of the existing antidepressant drug.[4,5]

Augmentation therapy includes adding a second drug, which is not an antidepressant, to current drug therapy. Augmentation may be done at the onset of depression to speeding up the antidepressant effects or to increase the likelihood of achieving remission and following the use of standard antidepressants when it fails to achieve remission.[5] Many agents are used as augmenting agents like lithium, thyroid hormones, atypical antipsychotics, dopamine agonists, anticonvulsants, psychostimulants, sex steroids, glucocorticoids. Few antipsychotics that have been successfully tried for augmentation with SSRIs and SNRIs are olanzapine, aripiprazole, quetiapine, and ziprasidone.[5]

Very few studies have been conducted worldwide, evaluating the role of ziprasidone and quetiapine as augmentation agents in MDD patients showing partial response to antidepressant drugs. Still, no study has shown comparison between the two agents and none have been conducted in the Indian population which made basis for conducting this study.

MATERIAL AND METHODS

Study design and patient population

It was a prospective, open-label, randomized, and comparative clinical Study, conducted by the Department of Pharmacology and Department of Psychiatry, Pt. B.D. Sharma PGIMS, Rohtak (Haryana). The study was conducted after getting approval from institutional ethics committee (wide letter no. IEC/18/Pharma04 dated 19.12.18) of Pt. B.D. Sharma PGIMS, Rohtak (Haryana). The study was conducted following Good Clinical Practice (GCP) and the Declaration of Helsinki. All the patients were screened and selected as per the predefined inclusion and exclusion criteria, and informed consent was obtained from all the participants.

Inclusion criteria

1. Patients aged 18 years to 55 years of either gender.
2. Patients who meet criteria for major depressive disorder (MDD), as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5)[6], and with inadequate clinical response to escitalopram 20mg per day for 6 weeks.
3. HAM-D score of 15 or more on 17 item version, at the screening of the study.
4. Patient or his/her relative willing to provide written informed consent prior to enrolment in the study.

Exclusion criteria

1. Diagnosis of depression with psychotic features and bipolar disorder
2. Patient with a history of any chronic physical illness
3. Current psychoactive substance use disorders except for tobacco.
4. Pregnant women and lactating mothers.
5. Patient with a history of hypersensitivity to study drugs.
6. Inability to come for regular follow-ups.
7. Active suicidal ideation or other safety concerns
8. Exposure to drugs that interact with study drugs

Study procedure

a) An adequate number of patients (182) were screened and selected as per the inclusion and exclusion criteria for the study after giving escitalopram which was Part-I of the study. The enrolled patients were given detailed information about the purpose of the study and were provided with the patient information sheet, explaining the study procedures, risks, benefits, responsibilities, etc. Written informed consent was obtained from each patient. All patients were followed up for six weeks. During the study, patients were not permitted to take any non-study drugs.

b) An open-label trial of escitalopram (Part-I): Subjects diagnosed with MDD and were started on escitalopram (20mg/day O.D.) and were assessed weekly for improvement in depressive symptoms. Hamilton depression rating scale (HAM-D) scale for depression was used for evaluating response to escitalopram.

c) Open label trial of augmentation with Ziprasidone vs. Quetiapine (Part-II): After 6 weeks of treatment, the participants showing partial response, i.e., symptoms persisted and only 26-49% reduction in baseline severity of symptoms seen, were identified and enrolled

into Part-II of the study. During Part II of the study, augmentation was carried out with ziprasidone or quetiapine. Patients were randomly allocated to either treatment group (Group-A or Group-B) and were followed up for 6 weeks.

d) All the patients enrolled in the study was subjected to relevant clinical examination, and baseline parameters were recorded on 2, 4, and 6 weeks, by using a scale for assessment of the severity of depression – Beck's Depression Inventory (BDI) score.

Drug treatment

Group A: Escitalopram 20 mg tablet once daily plus quetiapine 200 mg tablet once daily.

Group B: Escitalopram 20 mg tablet once daily plus ziprasidone 20 mg capsule twice daily.

Efficacy assessment

Efficacy assessment was done using Beck depression inventory scale (BDI) for the study drug response at 2^{nd}, $4^{th,}$ and 6th week.

Safety assessment

It was carried out by doing an active adverse drug reaction (ADR) monitoring that was done using a predefined ADR form, based upon the known spectrum of adverse drug reactions with the study drugs to record any other ADR and when it happens. All the patients were subjected to ADR monitoring as and when these occurred during the study, including the Part- I and Part- II of study, specifically at 2^{nd}, 4^{th} and 6^{th} after starting the drug treatment. ADR monitoring was done by using the standard form of Central Drugs Standard Control Organization (CDSCO), which was subsequently uploaded in the WHO-UMC database using the VigiFlow software.[7]

Primary endpoint

1. Clinical response determined by reduction in Beck depression inventory (BDI) score.

RESULTS

Baseline characteristics regarding age, body weight, gender, were statistically similar in the two groups (Group-A & Group-B). The mean age of the patients in years was **37.70±00** and **42.80±00** years (Mean ± SEM) in Group A and B, respectively, mean body weight of patients in Group A was **65.35±00** and **59.65±00** in Group B, which were comparable. In Group A **45%** patients were males and **55%** were females whereas in Group B, **35%** patients were

males and **65%** were females. There was no history of drug allergy in patients in both the groups at baseline.

A total of 182 patients with symptoms of depression were screened and for Part-I of the study. Out of this, 122 patients showed adequate response to escitalopram (20 mg/day). The remaining 60 patients were enrolled in Part- II of the study for augmentation with the study drugs. Out of 60, 14 patients were excluded, as 10 patients did not fulfill the predefined inclusion criteria of the study and 4 did no follow up. The rest of the 46 patients who fulfilled all the criteria (figure 1), were randomized with the help of computer-generated random numbers and were allocated to either of the two treatment groups. Two patients in Group A and four patients in Group B were lost to follow-up who were dropped from the study, and the remaining 40 patients completed the treatment successfully.

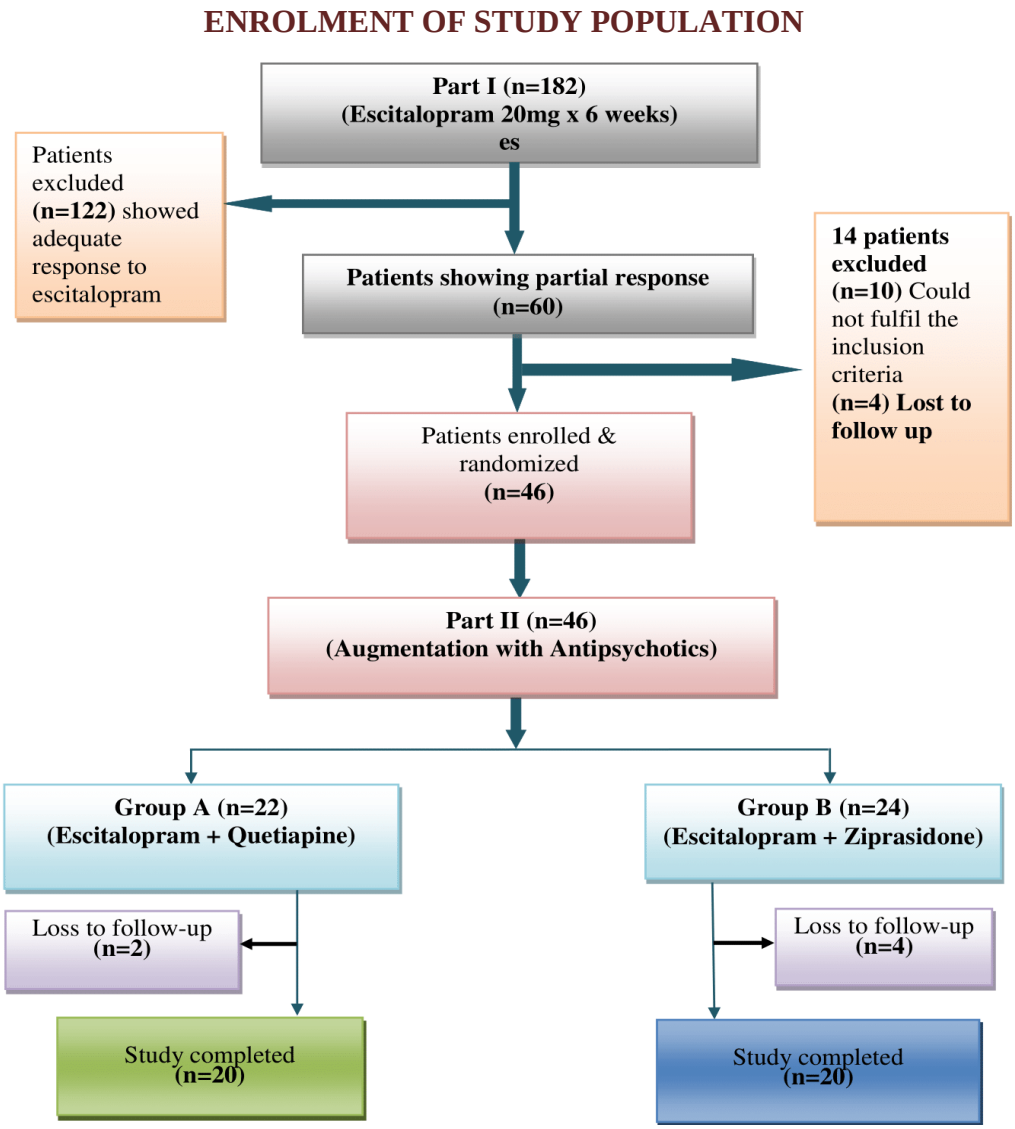


Figure 1: Enrollment of study population.

Beck depression inventory (BDI) scores: At baseline BDI score was (33.15 ± 0.678) in quetiapine group and (32.35±0.466) in ziprasidone group (**figure 2**). BDI score was significantly reduced to (23.65 ± 0.494) at 2 weeks, (16.10 ± 0.435) at 4 weeks and (11.40 ± 0.320) at 6 weeks in the quetiapine group whereas (22.80 ± 0.408) at 2 weeks, (15.35 ± 0.293) at 4 weeks, and (10.65 ± 0.233) at 6 weeks in ziprasidone group. The maximum reduction in the BDI scores was seen by the end of the study (at 6 weeks).

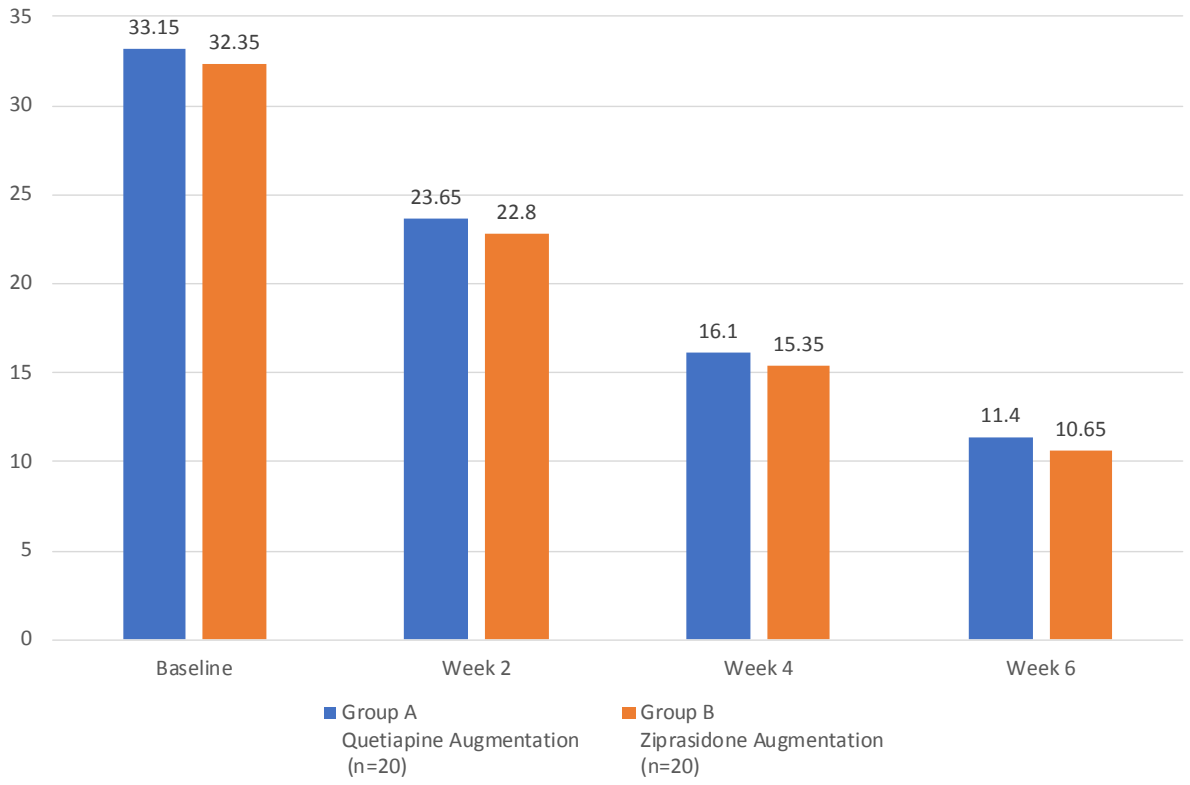


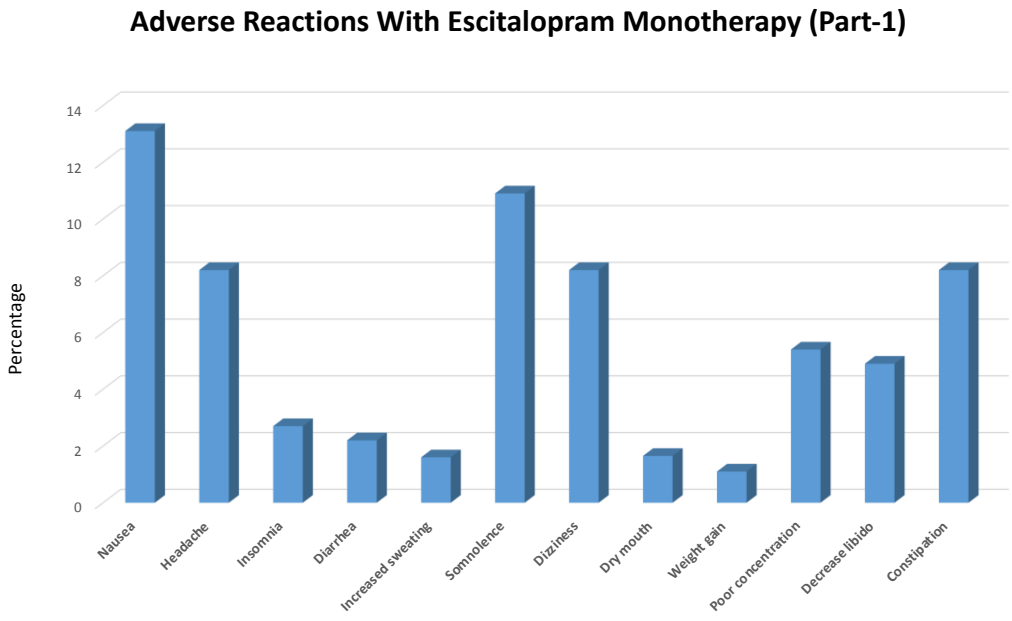
Figure 2: Changes in Beck depression inventory (BDI) scale.

Adverse drug reactions with escitalopram monotherapy: The patients were observed for the side effects like somnolence, dizziness, dry mouth, nausea, weight gain, diarrhea/loose stools, poor concentration, headache, etc. Patients were also inquired for any other side effects.

A total of 125 adverse events were observed with escitalopram monotherapy. The most common ADRs reported were nausea (n=24, 13.1%), somnolence (n=20, 10.9%), dizziness (15, 8.2%), constipation (15, 8.2%) and headache (15,8.2%). Other ADRs reported were, poor concentration (n=10), decrease libido (n=9), insomnia (n=5), diarrhoea (n=4), increased sweating (n=3), dry mouth(n=3) and weight gain (n=2).

All the adverse events were mild in severity and causality was assessed as probable. No patient discontinued the study medication due to adverse drug reactions in part I of the study.

After 6 weeks, 122 patients showed adequate response to escitalopram monotherapy and were excluded from the study. Remaining 60 patients, who showed inadequate response were enrolled in part II of the study and were given augmentation therapy with quetiapine or ziprasidone.

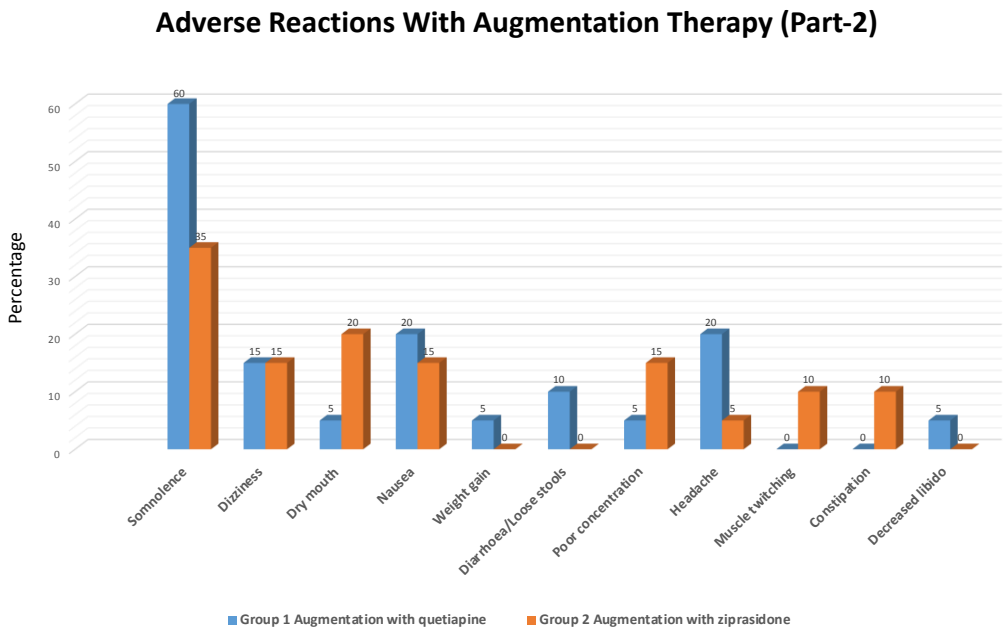


Adverse Drug Reactions with Anti-Psychotic Augmentation

The patients were observed for the side effects like somnolence, dizziness, dry mouth, nausea, weight gain, diarrhea/loose stools, poor concentration, headache, etc. Patients were also inquired for any other side effects.

A total of 54 adverse events were observed in both the groups. The most common ADRs in Group 1 were somnolence (n=12, 60%), headache (n=4, 20%) and nausea (n=4, 20%). Other ADRs reported were, dizziness (n=3), dry mouth (n=1), weight gain (n=1), diarrhea (n=2) and poor concentration (n=1) and decreased libido (n=1).

Sedation (n=7, 35%), dry mouth (n=4, 35%) and dizziness (n=3, 15%), nausea (n=3, 15%), and poor concentration (n=3, 15%) were the most common ADRs in patients of Group 2. Other ADRs reported were muscle twitching (n=2), constipation (n=2), headache (n=1).



SEVERITY

The severity of the ADRs was graded according to the Division of AIDS (DAIDS) scale for grading the severity of adult and pediatric adverse events, version 2.0. In this study, all the ADRs observed were Mild, i.e., Grade I. The ADRs caused no or minimal interference with usual social and functional activities with no intervention indicated.

Comparison of Severity of adverse drug reactions in both groups

Severity Grade	Group A	Group B
Mild	29	25
Moderate	Nil	Nil
Severe	Nil	Nil
Potentially life-threatening event	Nil	Nil
Death	Nil	Nil

DISCUSSION

Depression is a chronic mental and public health disorder that encompasses multiple psychobiological syndromes. The characteristic features of depressed mood, anhedonia, hopelessness, or feeling of worthlessness or guilt may be associated with cognitive and somatic disturbances, causing profound functional impairment.

Since the diagnosis of MDD is mainly clinical, several scales are used for a more objective assessment of the onset and severity of symptoms. These scales may be clinician-administered or self-administered, and are interpreted in context of MDD severity, prognosis

and monitoring of the symptoms. Multiple, validated and well-established scales such as HAM-D, CGI, BDI etc. are available and are chosen by the physician based on the patient and practice setting. Current treatment modalities rely on a combination of clinical observation, psychometric analysis, and the patients' neuropsychopharmacology. Psychiatrists and other medical practitioners, trained extensively in the medical model of mental illness, often prefer to manage depression with medication.[8]

About 30 percent patients do not respond to standard antidepressant medications alone. The available guidelines provide treatment strategies to manage partial and non-response to treatment using optimization, switching, augmentation and combination treatment. Augmentation includes using various medications in conjunction with antidepressants, to enhance the effect of antidepressants. Some important augmenting agents include lithium, thyroxine, lamotrigine, valproic acid, typical antipsychotics like haloperidol and chlorpromazine, and atypical antipsychotics like olanzapine, risperidone, aripiprazole, quetiapine and ziprasidone.[9]

The present study was done in patients aged 18 to 55 years, diagnosed with MDD and showing inadequate response to Escitalopram 20mg after 6 weeks of treatment. All the patients were assessed in terms of efficacy of the treatment along with its safety. The observations of this study showed that the baseline study population characteristics in both the groups were comparable ($p>0.05$). So, the population characteristics did not have any influence on the study outcomes. The patients were subjected to the following observations for efficacy and safety assessment.

Efficacy assessment was done by observing improvement in scores, Beck's Depression Inventory (BDI)[10] at the end of 2,4 and 6 weeks of augmentation with antipsychotics.

Analysis of BDI scores showed a statistically significant reduction in both groups' scores compared to baseline at 2, 4, and 6 weeks, with greater reduction in score seen with Ziprasidone augmentation. However, both augmentation therapies were equally effective in reducing depressive symptoms in study population, with statistical significance lacking with respect to one another.

In the present study both augmentation agents showed similar side effects profile. However, the number of ADRs was lesser in the ziprasidone group, suggesting better tolerability and

patient compliance. A study on quetiapine augmentation found that sedation, dry mouth and dizziness were the common ADRs and weight gain was found in 40% of patients.[11]

In anoher study by on ziprasidone augmentation of escitalopram for MDD, somnolence, akathisia, muscle twitching, GI upset and dry mouth were the common ADRs observed. Other adverse events were poor concentration, headache, and anxiety.[12]

Therefore, it can be ascertained that quetiapine and ziprasidone augmentation to escitalopram reduce various scores used for symptom and severity evaluation of MDD.

CONCLUSION

The augmentation of escitalopram, an SSRI, with atypical antipsychotics like quetiapine and ziprasidone in MDD patients showing a partial response causes a significant improvement in the depressive symptoms and results in an overall improvement in the QOL. Since the atypical antipsychotics and SSRIs act via different receptors, with distinct pharmacological actions to achieve therapeutic benefits in partial responders of MDD, it may be good to augment the SSRIs with atypical antipsychotics to gain better symptom control with improved compliance. The present study showed similar efficacy and safety when quetiapine or ziprasidone was used as an add-on therapy to escitalopram over 6 weeks. Quetiapine and ziprasidone are less tried and may open new vistas to treat the patients who respond inadequately to routine treatment with SSRIs.

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