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Original Article

Augmentation of Low-dose Atypical Antipsychotics along with Antidepressant in Mild-to-Moderate Depression – A Case–control Study

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Abstract

Introduction: Depression is the most common mental disorder in the world today, affecting 34 crore people in the world. 1:4 women and 1:10 men will develop depression sometime in their lifetime, 50% of cases are unrecognized. Various studies have shown adding our augmenting antidepressant with low-dose antipsychotic requires only in case of bipolar depression, recurrent depression, or resistant depression. Anxiety commonly associated with most of the depressive patients.

Aim: This study aims to study augmentation of low-dose atypical antipsychotics along with antidepressant in mild-to-moderate depression.

Materials and Methods: In this case–control study, mild-to-moderate depression cases were divided into 50 patients in each group. The study group treated with augmented antidepressant with low-dose antipsychotic olanzapine or amisulpride or quetiapine or levosulpiride or risperidone and in the control group treated with one or two different groups of antidepressant. Benzodiazepam has not been used in either of the group. Depression was diagnosed after meeting criteria as per DSM-5 (diagnostic and statistical manual of mental disorders) by clinical evaluation by a psychiatrist. The scale used was the Beck Depression Inventory scale for severity of depression, Brief Psychiatric Rating Scale to rule out any psychotic symptoms.

Results: Mean age of the control group was 32.48 ± 6.66 years and in the study group 33.22 ± 7.09 years (P = 0.0.592). Mean remission of the control group was 31.14 ± 3.55 days and in the study group 23.38 ± 2.42 days (P < 0.0001). Mean hospital stay of the control group was 44.16 ±3.91 days and in the study group 28.52 ± 1.82 days (P < 0.0001).

Conclusion: Augmentation of low-dose atypical antipsychotics along with standard antidepressants reduces the period of hospital stay and early remission from depressive symptoms.

Key words: Antidepressant, Augmentation, Combination, Depression

INTRODUCTION

Today, depression is the world's most prevalent mental illness, affecting 34 crore individuals in the world. Sometime in their lifetime, 1:4 women and 1:10 men may experience depression. This is unfortunate since one of the most treatable mental disorders is depression.[1] Substantial impairment is induced by depressive disorders, sometimes beyond that resulting from other chronic conditions such as cardiac disease and diabetes.[2] In the treatment of the major depressive disorder, atypical antipsychotic treatments are commonly utilized. There were an estimated 3.9 million treatment visits each year in the United States in 2007 and 2008 in which an antipsychotic medication was administered for depression, and almost all of these (96 percent) included the prescription of an atypical antipsychotic drug.[1] While aggregate figures obscure the precise indications for use (i.e., monotherapy vs. adjunctive therapy), this reprehensive therapy results are also consistent with industry market reports.[2] The US Food and Drug Administration has approved three atypical antipsychotic drugs as adjunctive treatments in adults for depression, although none are approved for monotherapy. These approvals (and subsequent marketing efforts), along with the number of prescriptions, indicate that adjunctive

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therapy utilizes a significant number of prescriptions for atypical antipsychotic drugs written for the treatment of depression.[3-5]

Over the last couple of decades, several antidepressant medicines have been established, but the mechanism of action of these medicines remains uncertain, and the proportion of patients who are not helped by these medicines remains large. Treatment with antidepressants and antipsychotics (including conventional antipsychotics, such as sulpiride, or atypical antipsychotics, such as clozapine, olanzapine, quetiapine, aripiprazole, risperidone, and ziprasidone) can involve the complete resolution of all symptoms of depression using several drugs with different mechanisms of action.

Various studies have shown adding our augmenting antidepressant with low-dose antipsychotic requires only in case of bipolar depression, recurrent depression, or resistant depression. Most of the psychiatrists still avoid augmenting antipsychotic in mild-to-moderate depression.

Aim

This study aims to study augmentation of low-dose atypical antipsychotics along with antidepressant in mild-to-moderate depression.

MATERIALS AND METHODS

This case–control study was conducted in the department of psychiatry of a large tertiary care hospital in Hyderabad with the urban population for 2 years from the year 2017 to 2019.

The required sample size is 100, in which 50 in the study group and 50 in the control group had been chosen randomly.

Inclusion Criteria

Selection criteria were the age group of 20–50 years, male, not on any psychoactive substance abuse, no family history of psychiatric illness, and no history of mental illness, no history of recent death or grief in the family, and no h/o any comorbid physical or surgical illness.

Exclusion Criteria

Those who have a history of substance abuse, a recent death in the family, family history of mental illness or suicide history in the family and recent death or grief in family, severe depression and too severe depression after clinical evaluation, depression with psychotic symptoms, recurrent depression, or bipolar depression were excluded from the study. Female patients were not included in this study because of the unavailability of inpatient female treatment.

The study group consisted of 50 patients of mild-to-moderate depression augmented antidepressant with low-dose antipsychotic olanzapine or amisulpride or quetiapine or levosulpiride or risperidone in randomly selected depression cases. The control group consisted of 50 patients, primarily case of depression mild to moderate and was exposed to one or two different groups of antidepressant. Benzodiazepine has not been used in either of the group.

After ethical clearance from all participants, informed consent had been taken, all participants examine by principal investigator who was blinded to the beck depression inventory (BDI) score, diagnosis made as per DSM-5.[6] Selected participants were subjected to a screening questionnaire BDI.[7] In BDI, score 11–18 considered as mild depression, score 19–25 considered as moderate depression, and any score 25 or above is severe or extreme severe depression.

Those who were selected assigned randomly in the study and control groups each of 50 patients over the next 2 years. After discharge from hospital, follow-up of all cases has been done for more than 8 months. In the study group, atypical antipsychotic gradually tapered down over the next 6–8 months and continued with a single antidepressant in adequate tolerable dose. The study group has been exposed to antidepressant mainly Cap fluoxetine 20 mg, Tab sertraline 50–150 mg, Cap venlafaxine 75–150 mg, and Tab mirtazapine 30 mg, with low-dose antipsychotics mainly; olanzapine (2.5–5 mg)/amisulpride (50–100 mg)/levosulpiride (50–100 mg) or Tab quetiapine (50–100 mg) and Tab risperidone (1 mg) randomly by the psychiatrist. No benzodiazepine has been added.

In the control group, single or combination of antidepressant had been added depends on the response after 21 days. The antidepressant used was mainly either of, Cap fluoxetine 20 mg or Tab sertraline 50–150 mg or Cap venlafaxine 75–150 mg or Tab mirtazapine 30 mg and if no response after 21 days second antidepressant use either of different drug of earlier mentioned antidepressant or Cap Doxepin (75–150 mg), in maximum recommended and tolerable dose. No benzodiazepine had been added in the control group also.

Remission has been considered after clinical examination by psychiatrist blinded to BDI score and further confirmed it with BDI score, reduced in BDI score <6 or 100% symptoms free, discharge has been considered, that is, hospital stay when the patient felt comfortable and self-reported for discharge and after clinical evaluation by two psychiatrists.

Statistical analysis was done by using SPSS Version 21 software. Pearson Chi-square used to calculate the

association of categorical variable and independent Student's t-test used to compare the continuous variables.

RESULTS

In this study, 100 male patients with mild-to-moderate depression were divided into two groups study and control, each group with 50 patients. No statistical difference noted between age in the control group and study group. A higher number of patients were in 31–40 years age group (48%). In the control group, 46% of patients and in the study group, 48% of patients are between 31 and 40 years age group. Mean age of the control group was 32.48 ± 6.66 years and in the study group 33.22 ± 7.09 years, statistically insignificant ($P = 0.592$) [Table 1].

In this study, 12% of patients were in the range of BDI score 11–15, 42% of patients were in the range of BDI score, and 42% of patients were in the range of BDI score 21–25. There is no statistical difference noted between BDI score in both groups. In the control group, 20% of patients were in the range of BDI score 11–15, 46% of patients in the range of BDI score 16–20, and 34% of patients were in 21–25 BDI score and study group 38% of patients were in 16–20 BDI score, and 34% of patients were in the range of BDI score 21–25, statistically insignificant ($P = 0.234$). Mean BDI score of the control group was 19.02 ± 3.62 and in the study group 20.06 ± 3.62 statistically insignificant ($P = 0.155$) [Table 2].

In this study, 36% of patients in mild depression in the control group and 30% of patients were in mild depression in the study group, 64% of patients were in moderate depression in the control group, and 70% of patients were in moderate depression in the study group [Table 3].

Mean remission of the control group was 31.14 ± 3.55 days and in the study group 23.38 ± 2.42 days ($P < 0.0001$). In this study, 50% of patients had remission in <30 days, in the study group, 100% of patients have had remission in <30 days, and in the control group, 86% of patients had remission in 31–40 days, statistically significant ($P < 0.0001$) [Table 4].

Mean hospital stay of the control group was 44.16 ± 3.91 days and in the study group 28.52 ± 1.82 days ($P < 0.0001$). In this study, 50% of patients had discharged in <30 days, in the study group, that is, 100% of patients were had discharged in <30 days. In the control group, 18% of patients discharge in 31–40 days, 72% of patients had discharged in between 41 to 50 days, and 10% discharge in 51–60 days, statistically significant ($P < 0.0001$) [Table 5].

About 100% of patients among the study group and 100% of patients of the control group could be followed up for next 1 year, and it was found out of 50 patients in the study group only 2 patients had a relapse of symptoms in 1 year and out of 50 patients of the control group 13 patients had a relapse of symptoms over 1 year. There is no drop out in either of the group during follow-up. Over 4–6 months, atypical antipsychotics gradually stopped, and the study group patient continued with a standard maintenance dose of single antidepressant. The control group patient continued with the same medication with the rationalization of dose as per evaluation during clinical follow-up. No patient in either of the group reported with any significant side effect or problem with medication. The main reason for relapse was stopping the medication when they were feeling better. Hence, it was difficult to say either of the group has any tendency for relapse because of poor drug compliance or unsupportive environment stressor among the study and control groups.

DISCUSSION

Depression is one of the common illnesses. Depending on the severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe. In India, the National Mental Health Survey 2015–2016 reveals that nearly one in 20 Indian suffers from depression.[8]

In this study, we found no statistical difference noted between age in the control group and study group. There

Table 1: Age-wise distribution of the control and study groups

Group	Age group				Total	*P*-value
	<30	31–40	41–50	>51		
Control						
Count	20	23	6	1	50	0.592
% within group	40.00%	46.00%	12.00%	2.00%	100.00%	
Study						
Count	19	25	4	2	50	
% within group	38.00%	50.00%	8.00%	4.00%	100.00%	
Total						
Count	39	48	10	3	100	
% within group	39.00%	48.00%	10.00%	3.00%	100.00%	

Table 2: BDI score range in the control and study groups

Group	BDI score			Total	*P*-value
	November 15	16–20	21–25		
Control					
Count	10	23	17	50	0.155
% within group	20.00%	46.00%	34.00%	100.00%	
Study					
Count	6	19	25	50	
% within group	12.00%	38.00%	50.00%	100.00%	
Total					
Count	16	42	42	100	
% within group	16.00%	42.00%	42.00%	100.00%	

Table 3: Diagnosis in the control and study groups

Group	Diagnosis		Total
	Mild depression	Moderate depression	
Control			
Count	18	32	50
% within group	36.0%	64.0%	100.0%
Study			
Count	15	35	50
% within group	30.0%	70.0%	100.0%
Total			
Count	33	67	100
% within group	33.0%	67.0%	100.0%

Table 4: Remission in the day in the control and study groups

Group	Remission in days when BDI-0			Total	*P*-value
	<30	31–40	41–50		
Control					
Count	0	43	7	50	<0.0001
% within group	0.0%	86.0%	14.0%	100.0%	
Study					
Count	50	0	0	50	
% within group	100.0%	0.0%	0.0%	100.0%	
Total					
Count	50	43	7	100	
% within group	50.0%	43.0%	7.0%	100.0%	

is no statistical difference noted between BDI score in both groups. In this study, 36% of patients in mild depression in the control group and 30% of patients were in mild depression in the study group, 64% of patients were in moderate depression in the control group, and 70% of patients were in moderate depression in the study group. Mean remission of the control group was 31.14 ± 3.55 days and in the study group 23.38 ± 2.42 days ($P < 0.0001$). In the control group, 18% of patients discharge in 31–40 days, 72% of patients had discharged in between 41–50 days, and 10% discharge in 51–60 days, statistically significant ($P < 0.0001$).

Table 5: Hospital stay/discharge from the hospital in the control and study groups

Group	Hospital stay/discharge in days				Total	*P*-value
	<30	31–40	41–50	51–60		
Control						
Count	0	9	36	5	50	<0.0001
% within group	0.0%	18.0%	72.0%	10.0%	100.0%	
Study						
Count	50	0	0	0	50	
% within group	100.0%	0.0%	0.0%	0.0%	100.0%	
Total						
Count	50	9	36	5	100	
% within group	50.0%	9.0%	36.0%	5.0%	100.0%	

Low-dose atypical antipsychotics along with one standard antidepressant medicine reduced the remission time and reduced hospital stay compared to the control group who were on single or two different antidepressants with maximum recommended and tolerable dose. However, there is no statistically significant difference in mean BDI score of control and significant group.

Most of the study based on the augmentation of atypical antipsychotics in major or treatment-resistant depression. This is the first study which has been done to observe the effect of low-dose augmentation of atypical antipsychotics along with standard antidepressant from day 1 without adding benzodiazepine not only reduces the remission time but also decreases hospital stay, that is, discharge from hospital and found statistically significant result compare to control group those were on either one or two standard antidepressants without benzodiazepine, in mild-to-moderate depression.

Result of this study is in agreement with the study of the American Psychiatric Association 3rd Edition Practice Guidelines which was published in 2010.[9] They reported that adjunctive treatment with an atypical antipsychotic agent was significantly more effective than placebo in terms

of response and remission. The Canadian Network of Mood and Anxiety treatment guidelines were updated in 2016.[10] This guideline recommends adjunctive treatment with atypical antipsychotics as follows; aripiprazole, quetiapine, and risperidone are first lines, brexpiprazole and olanzapine second line, and ziprasidone third line. The NICE guidelines for the treatment of major depression[11] recommend adjunctive treatment as a treatment option and consider atypical antipsychotics such as aripiprazole, quetiapine, risperidone, and olanzapine, to be appropriate adjunctive treatment agents.

German National Clinical Practice Guidelines[12] are more conservative, not recommending atypical antipsychotics as an adjunctive treatment except in psychotic depression. However, the MPG (Max Planck Institute of Psychiatry) in German included quetiapine as a first-line, well-tolerated augmenter with a good evidence base, advising that it should be used in addition to an SSRI or serotonin-norepinephrine reuptake inhibitors. They advised that quetiapine is possibly more significant than lithium.

The World Congress of Biological Psychiatry included quetiapine as a first-line option, referencing a study in which it was significantly more effective than antidepressant monotherapy, though it has been associated with more weight gain and sedation (Komossa *et al*., 2010; Bauer *et al*., 2010).[13,14] Clinical studies in naturalistic settings consistently indicate that barely half of the depressed patients respond to initial antidepressant monotherapy (the most common recommendation in practice guidelines) and that only one third eventually achieve satisfactory remission of symptoms (the desired goal in most guidelines).[15] Shelton *et al*. reported that a combination of fluoxetine and olanzapine was superior to either drug alone in their non-psychotic depressed sample.[4]

Reviewing all the recommended studies of the different country this study is in close agreement that augmenting low-dose antipsychotics with standard antidepressant along with supportive therapy from day 1 not only helps in early remission but also reduces the hospital stay duration. Since this study population was less so it needs further study in the larger population without gender bias to formulate treatment guidelines and remove the stigma that atypical antipsychotics can only be used in treatment-resistant depression, major depression or depression with psychotic symptoms seeing the role of atypical antipsychotics in all type of receptors which help in early relief from depressive symptoms.

CONCLUSION

There was a significant improvement on remission in patients augmented with low-dose atypical antipsychotic along with one antidepressant from day 1 and reduced in the day of hospital stay with antidepressant augmented with low-dose atypical antipsychotics. At present, side effects are more predictable than treatment efficacy, so the relative risk of different types of side effects is the most important factor to consider. Future studies need to identify subgroups of depressive patients, categorized by genetics, neurophysiological markers, or family history.

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