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AUGMENTATION OF LOW DOSE ANTIPSYCHOTICS REDUCED HOSPITAL STAY IN MILD TO MODERATE DEPRESSION

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 life time. 50% of cases are ***unrecognized***. This is sad because depression is one of the most treatable mental illnesses.

At any time 2 – 4 % of the population are suffering from depression. It has a high prevalence among people suffering from diseases such as IHD, Stroke, Epilepsy, Diabetes, Cancers, HIV positive/AIDS affected individuals. Females are affected twice as often as males.

Various study has shown adding our augmenting antidepressant with low dose antipsychotic require only in case of Bipolar depression, Recurrent Depression or resistant depression.

Most of the Psychiatrist still avoids augmenting antipsychotic in MILD TO moderate depression. Anxiety commonly associated with most of depressive patients.

My aim of study to show how augmentation of low dose Olanzapine in range of 2.5. to 5 mg daily or Amisulpride /Levosulpride/Quitiapine(25 to 100) mg not only achieved remission early and decreased hospital stay with reduces relapse in future.

Study group consist of 50 pt case of Mild to Moderate Depression augmented antidepressant with low dose antipsychotic olanzapine or amisulpride, Quitiapine or levosuloride in randomly selected Depression cases.

Control group consist 50 pt primarly case of Depression Mild to Moderate and were exposed to one or two different group of anti depressant.

Benzodiazepam has not been used in either of group.

Scale used were Beck Depression inventory scale, Hamilton anxiety and depression scale, Brief Psychiatric rating scale to ruled out any psychotic symptoms.

Selection criteria were age group 25 to 40 yrs, male , not on any psychoactive substance abuse, No family history of psychiatric illness, no past history of mental illness ,no history of recent death or grief in family. Pt wit Severe depression BDI Score 30 and above,Depression with psychotic symptom and Recurrent depression has been excluded. All cases were freshly diagnosed and

first time reported with symptoms.Female patient has not been included in study as in centre where study has been conducted no provision of female inpatient facility in psychiatry ward was available.

Study has been conducted in period of three yrs and follow up of 80% patient for 1 yrs.

Review of literature- Atypical antipsychotic medications are widely used in the treatment of major depressive disorder. In the United States in 2007 and 2008, there were an estimated 3.9 million treatment visits per year in which an antipsychotic medication was prescribed for depression, and nearly all of these (96%) involved prescription of an atypical antipsychotic medication [1]. Although aggregate statistics mask the specific indications for use (i.e., monotherapy versus adjunctive therapy), this represents a substantial increase in antipsychotic treatment of depression over time, as there were just over 2 million such visits annually during 1995 and 1996, of which 405,000 involved prescriptions for atypical antipsychotic medications. These data are also consistent with market reports from industry [2]. Three atypical antipsychotic medications have approval from the US Food and Drug Administration (FDA) as adjunctive therapies in depression for adults, while none are approved for monotherapy. These approvals (and subsequent marketing efforts), along with the volume of prescriptions, suggest that a large number of prescriptions for atypical antipsychotic medications written for the treatment of depression are being used for adjunctive therapy [3]–[5].

The efficacy of adjunctive atypical antipsychotic therapy in reducing depression symptom severity in major depressive disorder is summarized in two previous systematic reviews, but neither comprehensively summarized data on both efficacy and safety [6],[7]. Both reviews analyzed efficacy only in terms of dichotomous response and remission outcomes derived from clinician-rated depression measures and did not assess changes in terms of symptom severity on the underlying continuous rating scales

of The National Library of Medicine's MEDLINE database was searched for all English-language articles published from January 1966-December 2011 describing the use of atypical antipsychotics in treatment-resistant depression. The literature retrieved was limited to case series, open-label trials, and randomized controlled trials (RCT). Studies of bipolar depression, psychotic depression, or studies conducted in children and adolescents were excluded. Thirty-five studies using atypical antipsychotics for augmentation treatment of depression were included in this analysis. Trials were identified for aripiprazole (six open-label; three RCT), clozapine (one case series), olanzapine (three open-label, including two case series; four RCT), quetiapine (four open-label; five RCT), risperidone (two open-label; five RCT), and ziprasidone (two open-label). The atypical antipsychotics may be effective as adjunctive therapy in MDD; however, their adverse effect profile may be unfavorable to some patients. Trying at

least one alternative treatment strategy after an initial antidepressant is indicated before augmentation is implemented with these agents.(8)

WHAT IS DEPRESSION-

Sadness is a universal emotion that no one is immune from, everyone in the world feels sad in some way or another on a daily basis for various reasons. Actually as generally believed its not always as tumultuous as the general public believes, but it's a time of great change which can in some cases or over a period of time develop symptoms of depression ,emotion disturbances or problems ,anxiety disorder and the list goes on. The state of feeling sad is called "Depression" and usually refers to a condition of feeling sad very often, for a prolonged period of time. Depression is defined as an illness when the feelings of depression persist and interfere with a individual's ability to function. Depressive disorders consist of a group of pathologies with a high and growing prevalence in the general population.

2. According to the World Health Organization, in the next two decades there will be a dramatic change in health needs of the world population, due to the fact that diseases like depression and cardiac disorders are substituting the traditional problems of infectious diseases and malnutrition. The damage caused by diseases measured by the

Disability Adjusted Life Years shows that major depression, the 4th generative cause of overload in 1990, will be the 2nd cause in 2020, only losing to cardiac (Bahls 1999 and 2002; Murray & Lopez 1996).(1,2)

3. How dose medicine acts-

Olanzapine,Quitiapine,Amisulpride and levosulpride has a higher affinity for 5-HT_{2A} serotonin receptors than D_2dopamine receptors, which is a common property of all atypical antipsychotics, aside from the benzamide antipsychotics such as amisulpride. Olanzapine also had the highest affinity of any second-generation antipsychotic towards the P-glycoprotein in one *in vitro* study.[61]P-glycoprotein transports a number of drugs across a number of different biological membranes including the blood-brain barrier, which could mean that less brain exposure to olanzapine results from this interaction with the P-glycoprotein.

5-HT_{2A}	2.4	Inverse agonist. May underlie the "atypicality" of the newer antipsychotics like olanzapine. May contribute to sedating effects
5-HT2C	10.2	Inverse agonist. May underlie the appetite-stimulating effects of olanzapine.

- Oral formulation combined with fluoxetine: treatment of acute depressive episodes associated with bipolar I disorder in adults, or treatment of acute, resistant depression in adults

Moreover, most of the atypical antipsychotics have a large action spectrum, beyond the only dopamine receptors: their effects on the serotonin receptors--particularly the 5-HT2A and 5-HT2C receptors--suggest that their association to SSRI could be a promising treatment for depression. Indeed, SSRI act mainly by increasing the serotonin level in the synapse,

thus leading to a non specific activation of all pre- and post-synaptic serotonin receptors. Among them, 5-HT2A/2C receptors have been involved in some of the unwanted effects of SSRI: agitation, anxiety, insomnia, sexual disorders, etc. The inhibition of these receptors could be thus beneficial for patients treated with SSRI. **Amisulpride is an unique atypical antipsychotic that selectively blocks dopamine receptors presynaptically in the frontal cortex, possibly enhancing dopaminergic transmission.** The antidepressant effect of amisulpride was shown in dysthymia in many clinical studies versus placebo, tricyclic antidepressants, SSRI or others. However, a shorter delay for symptom relief was not demonstrated for amisulpride as compared to comparative antidepressants. Other atypical antipsychotics (clozapine, olanzapine), which act on a large variety of receptors, have shown antidepressant effects--mainly in association with SSRI--in different psychiatric diseases: treatment-resistant major depression, major depression with psychotic symptoms and depression of bipolar disorders, with no increase of manic symptoms in this latter case. Moreover, the delay for symptom relief was greatly shortened.(8)

How Antidepressants Work

Most antidepressants are believed to work by slowing the removal of certain chemicals from the brain. These chemicals are called neurotransmitters (such as serotonin and norepinephrine). Neurotransmitters are needed for normal brain function and are involved in the control of mood and in other responses and functions, such as eating, sleep, pain, and thinking.
Antidepressants help people with depression by making these natural chemicals more available to the brain. By restoring the brain's chemical balance, antidepressants help relieve the symptoms of depression.

Specifically, antidepressant drugs help reduce the extreme sadness, hopelessness, and lack of interest in life that are typical in people with depression. These drugs also may be used to treat other conditions, such as obsessive compulsive disorder, premenstrual syndrome, chronic pain, and eating disorders.
Typically, antidepressants are taken for 4 to 6 months. In some cases, however, patients and their doctors may decide that antidepressants are needed for a longer time.

OBJECTIVES

STUDY OF AUGMENTATION OF LOW DOSE ATYPICAL ANTIPSYCHOTIC WITH ANTIDEPRESSANT REDUCED HOSPITAL STAY IN MILD TO MODERATE DEPRESSIVE PATIENT

Material and Methods

STUDY POPULATION

Tertiary care hospital with Psychiatry center

AGE GROUP **25-40 yrs**

DESIGN OF THE STUDY **Prospective longitudinal study conducted over a period of 3 yrs (2013-2016)**

INCLUSION CRITERIA

Selection criteria were age group 25 to 40 yrs, male ,not on any psychoactive substance abuse, , No family history of psychiatric illness, no past history of mental illness ,no history of recent death or grief in family.No h/o any co morbid physical illness.

Study has been conducted in period of three yrs .

EXCLUSION CRITERIA

(1)Those who have history of substance abuse, recent death in family, family history of mental illness or suicide history in family and recent death or gerief in family, Severe depression ie BDI score more than 30 ,Depression with psychotic symptoms ,Recurrent Depression or Bipolar Depression. Female patients.

PROCEDURE

First phase (screening)

Study has been conducted over a period of three years at two hospitals at different phase.

Initially patient has been referred as a case of low mood or sadness. Beck Depression Inventory scale and Hamilton scale for anxiety has been to confirm the diagnosis of mild to moderate depression with or without anxiety symptoms .Patient with Severe depression has been excluded as to remove the stigma that low dose antipsychotic cannot be used in mild to moderate depression. Those having BDI cut off score of 10-29 and, Hamilton Anxiety score 18-30 has been considered as Depression with anxiety and has been added in study group. Brief psychiatric rating scale has been applied in both study and controlled group to exclude psychotic symptoms with depression. Any score positive in BPRS has been excluded from study group.

Second phase

Those who are selected for study has been assigned randomly in 50 each of two group over next 2 yrs till study group of 100 patient has been completed and follow up of 67 case has been done for more than 8 months. Study group has been exposed to anti depressant with low dose antipsychotics mainly ; Olanzapine/Amisulpride/Levosulpride or quitiapine randomly by psychiatrist. No Benzodiazepam has been added. Selection of study group has been done randomly.

In control group single or combination of antidepressant has been added depend on response after 15 days. No benzodiazepam has been added.

Remission has been considered reduced in BDI score by 100% and clinical evaluation by two different psychiatrist.

Discharge has been considered ie hospital stay when BDI score became zero along with clinical evaluation by two psychiatrists.

Data Analysis

The data obtained was analyzed using SSPS- software

STAGE 1

- **Study population profile –**

  BDI, Hamilton Anxiety Rating scale and BPRS score, (TABLE 1 -3)

  Prevalence of positive screened patient i.e. Patient with BDI score 10-29, Hamilton anxiety Rating Score 18-30 score and BPRS score-0 has been selected for study and randomly selected for study and controlled group.

STAGE-I

BDI Score

BDI Score of study population has shown in table 1. In study population 100 patients had BDI score Between 10-29, Hamilton Anxiety score for anxiety was 18-30 and BPRS score were zero.

Table 1: BDI Score group wise distribution of patients in study groups-

BDI score	Study group (%)	Controlled Group (%)	Total (%)
10-18	35(70)	32 (64)	67 (67)
19- 29	15 (30)	18 (36)	33 (33)
Total	50(100)	50 (100)	100 (100)

Table 2.-Hamilton Anxiety Rating Scale

HAM score	Study group (%)	Controlled Group (%)	Total (%)
<18	37(74)	40 (80)	77 (77)
18- 25	7 (14)	6 (12)	13 (13)
26-30	6(12)	4(8)	10(10)
Total	50(100)	50 (100)	100 (100)

3.Brief Psychiatric Rating Score

BPRS score	Study group (%)	Controlled Group (%)	Total (%)

	0	0	0
Total	50(100)	50 (100)	100 (100)

ASSOCIATION AMONG SCREENED POSITIVE PATIENT

For simplicity of description, in succeeding paragraphs, positively screened patients (BDI score 10-29), HAM score (18-30) and BPRS zero have been described as patient with screened positive for study and controlled group. Among these 100 patients 50 patients of two groups randomly selected for study and controlled group.

Study group has been given One antidepressant mainly Fluoxetine,Sertalline, Venlaflaxine,Mitrazapine or Escitalopram along with low dose atypical antipsychotic mainly; Olanzapine(2.5.to5mg) and Quitiapine (25mg to 100mg) or low dose Amisulpride and levosulpride in dose of 25mg to 100mg daily on divided dose. Benzodiazepam has not been used.

Among controlled group anti depressant mainly used were Cap Fluoxetine, Sertralline, Venlaflaxine, Mitrazapine ,Escitalopram, Doxepin, Dothiapin in combination or single depend upon tolerance and response of patients.(Maxium permissible dose and tolerable dose has been used single or in combination)

RESULT

Anti Depressant augmented with low dose antipsychotics in study Group and achievement of Remission ie 50% improvement and Hospital stay in days. Minimum day of achievement of remission in study group was 10 day and

maximum was 22days. Minimum day of hospital stay was 15 days and maximum

was 28 days,

TABLE-4.-

In controlled group not augmented with low dose anti psychotic and was one single or two different group of antidepressant

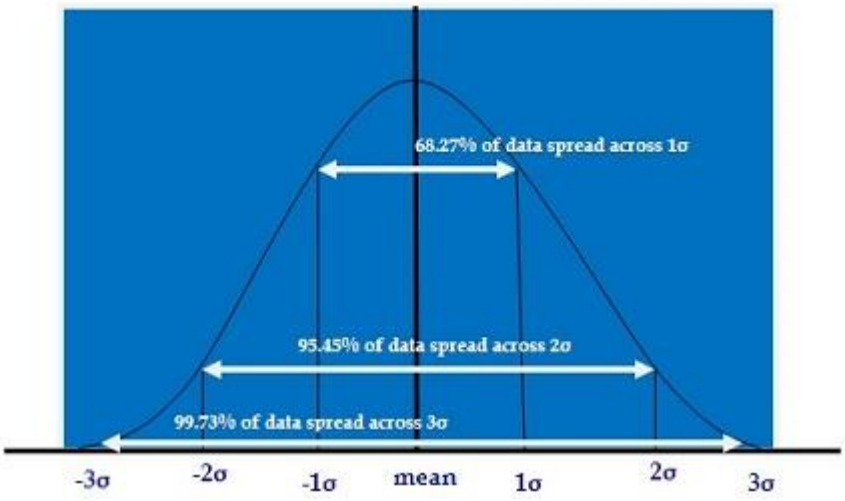
Controlled Group	Remission in days (MEAN)	Hospital stay ie sick leave in Days (MEAN)
50	28	36
Total	28	36

CONTROLLED GROUP

Minimum days of remission in control group in controlled group was 20days and maximum was 32 days. Minimum day of hospital stay was 28 days and maximum was 42 days.

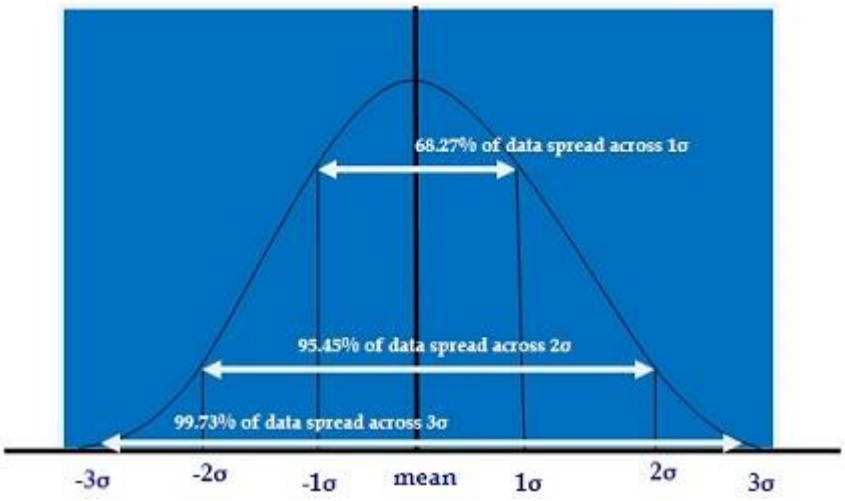
Remission in study group

The precise percentage values of the band of 1σ, 2σ, and 3σ are 68.27%, 95.45% and 99.73% respectively. The lower SD values closer to expected value gives the precise estimation.



No.of Samples	50
Mean	17.82
Standard Deviation	2.48825
Variance	6.19138

Remission For Compare group



Result

No.of Samples	50
Mean	28.12
Standard Deviation	2.6158
Variance	6.8424

Unpaired *t* test results

P value and statistical significance:

The two-tailed P value is less than 0.0001

By conventional criteria, this difference is considered to be extremely statistically

significant.

Confidence interval:

The mean of Group One minus Group Two equals -10.40
95% confidence interval of this difference: From -11.40 to -9.40

Intermediate values used in calculations:

t = 20.6412
df = 98
standard error of difference = 0.504

Group	Group One	Group Two
Mean	17.82	28.22
SD	2.49	2.55
SEM	0.35	0.36
N	50	50

Study has shown in two independent group of mild to moderate patient with augmentation of low dose antipsychotics mainly olanzapine/quitiapine/Amisulpride/levosulpride And only one or two Antidepressant in controlled group there is significant reduced of remission of symptoms in BDI score and psychiatric assessment in study group which was augmented with low dose of antipsychotics.

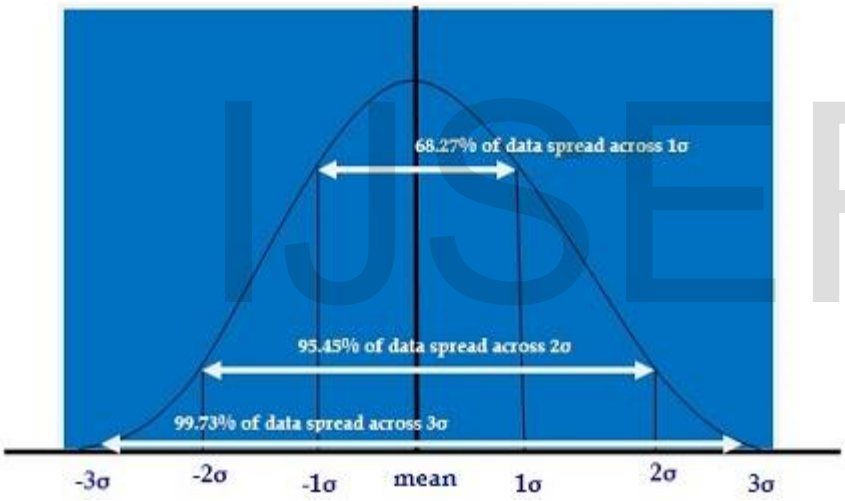
STUDY OF HOSPITAL STAY

Table 4: Comparison of Remission in days mean and hospital stay mean in days among study and controlled group

	Remission Mean in days	Hospital Stay Mean in days
Study Group	18	26
Controlled Group	28	36

For Study Group

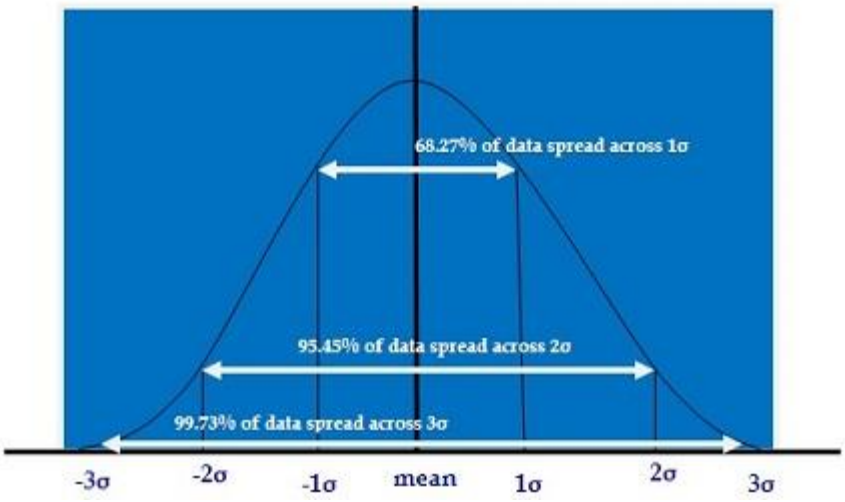
The precise percentage values of the band of 1σ, 2σ, and 3σ are 68.27%, 95.45% and 99.73% respectively. The lower SD values closer to expected value gives the precise estimation.



For compare group

The precise percentage values of the band of 1σ, 2σ, and 3σ are 68.27%, 95.45% and 99.73% respectively. The lower SD values closer to expected value

gives the precise estimation.



Group	Group One	Group Two
Mean	25.18	35.88
SD	2.23	3.56
SEM	0.32	0.50
N	50	50

Unpaired *t* test results

P value and statistical significance:

The two-tailed P value is less than 0.0001

By conventional criteria, this difference is considered to be extremely statistically significant.

Confidence interval:

The mean of Group One minus Group Two equals -10.70

95% confidence interval of this difference: From -11.88 to -9.52

Intermediate values used in calculations:

t = 18.0321

df = 98

standard error of difference = 0.593

Study has shown in two independent group of mild to moderate patient with augmentation of low dose antipsychotics mainly olanzapine/quitiapine/Amisulpride/levosulpride And only one or two Antidepressant in

controlled group there is significant reduced of hospital stay in study group which was augmented with low dose of antipsychotics mainly olanzapine/quitiapine/Amisulpride/levosulpride.

FOLLOW UP AND RELAPSE

70% of patients among study group and and 64% of patients of controlled group could be followed up for next 1 ½ yrs and it was found out of 40 patients in study group only 2 patient had relapse of symptoms in next one year and out of 32 patients of control group 10 patients had relapse of symptoms over next one year. Remaining of patient could not be followed up because of transfer of patient to different unit.

	Study Group follw up(35)	**Controlled Group follow up (32)**
Relapse in next one year	**2**	**10**

Main reason of relapse was stopping medication when they were feeling better, and non availability of drug while on leave or temporary duty.

So it was difficult to say either of group has any tendency for relapse because of drug among study and control group.

Conclusion-

(i)In this prospective longitudinal study study group augmented eithr atypical antipsychotcs mainly olanzapine,quitiapine,levosulpride and amisulpride along with anti depressand and control group was managed with single or two antidepressant ,both group benzodiazepam has not been used and BDI score and clinical assessment by two psychiatrist had been decided for remission and time of discharge from hospital in mild to moderate fresh case of Depression.. we found that augmenting antidepressant with low dose atypical antipsychotics not only stastically significant reduced the remission time but also reduced hospital stay compared to control group who were on single or two different antidepressant.

Taken together, our findings raise significant concerns regarding the impact of these medications in improving *overall* well-being. Although improvements in quality of life or functional status commonly co-occur with improvements in mild to moderate depression symptoms.

(ii) Taken together, our prospective longitudinal study found evidence of (1) significant reduced in number of day to achive remission in patients augmented with low dose atypical antipsychotic. (2)Significant reduced in day of hospital stay with antidepressant augmented with low dose atypical antipsychotics.

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