COVER PAGE

TITLE:

Efficacy and safety of low dose Amisulpride Versus Olanzapine-Fluoxetine Combination in the treatment of Post Schizophrenic Depression: A Randomised Controlled Trial

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STUDY PROTOCOL, STATISTICAL ANALYSIS PLAN & INFORMED CONSENT FORM

STUDY PROTOCOL

***FULL TITLE**:*
Efficacy and safety of low dose Amisulpride Versus Olanzapine-Fluoxetine Combination in the treatment of Post Schizophrenic Depression: A Randomised Controlled Trial

***BRIEF TITLE**:*
Low Dose Amisulpride Vs Olanzapine-Fluoxetine Combination in Post-Schizophrenic Depression (PSD-AOFC)

***SCIENTIFIC BACKGROUND**:*

About one-fourth of patients who have schizophrenia ultimately develop post-schizophrenic depression (PSD) with higher morbidity and mortality risks, including a higher number of suicides (1-2). Studies regarding the pharmacological treatment options for PSD are scarce. Very few clinical trials have been conducted with antipsychotics involving small study samples (3-4). Moreover, antipsychotics are Serotonin-Dopamine Antagonists, an action opposite to that of antidepressants (5), so their exact role in treating PSD needs further exploration. Antidepressants have been used in schizophrenia with depression but have shown little success (6). An antipsychotic along with an antidepressant (like an olanzapine-fluoxetine combination, OFC) is now the commonly practised treatment strategy in PSD. However, there is insufficient evidence in the literature confirming its rationality.

Studies have shown that amisulpride in a lower dose range (50-400 mg/day) has shown antidepressant actions (7). However, amisulpride has never been explored in PSD. Amisulpride monotherapy might have the added advantage of avoiding polypharmacy in these patients.

Also, correlating the clinical findings with changes in serum Brain-Derived Neurotrophic Factor (BDNF), a neuro-biomarker constantly studied in depressive conditions, would help substantiate the results (8). In our present study on PSD, we would like to corroborate the efficacy of the interventions (low-dose amisulpride versus OFC) with the changes in serum levels of BDNF.

NULL HYPOTHESIS:
There is no difference in the change in the Calgary Depression Scale for Schizophrenia (CDSS) scores between the study groups over 8 weeks.

ALTERNATE HYPOTHESIS:
There is a difference in the change in the Calgary Depression Scale for Schizophrenia (CDSS) scores between the study groups over 8 weeks.

AIM:

To compare the efficacy and safety of low dose Amisulpride Versus Olanzapine-Fluoxetine Combination and in patients with Post Schizophrenic Depression.

STUDY OBJECTIVES:

PRIMARY OBJECTIVES:

1. To evaluate the change in the severity of depression in terms of change in Calgary Depression Scale for Schizophrenia (CDSS) scores in the study groups over 8 weeks

SECONDARY OBJECTIVES:

1. To evaluate the change in symptom severity and improvement in terms of change in Clinical Global Impression (CGI) scores in the study groups over 8 weeks
2. To evaluate the change in serum BDNF levels in the study groups over 8 weeks
3. To determine the correlation (if any) between the changes in CDSS scores, CGI scores and serum BDNF levels
4. To detect adverse drug reactions (if any) and grading their severity

MATERIALS AND METHODS

STUDY SETTING:

The proposed study will be conducted at the Out-Patient (OP) and the In-Patient (IP) settings of the Department of Psychiatry, All India Institute of Medical Sciences, Bhubaneshwar.

STUDY DESIGN:

The proposed study will be a randomized, rater-blinded, controlled, clinical trial

STUDY PERIOD:

The study will be conducted within the time frame of two years.

STUDY POPULATION:

The proposed study will be conducted on the patients diagnosed with Post Schizophrenic Depression of the catchment area pertaining to AIIMS, Bhubaneswar.

INCLUSION CRITERIA:

All patients coming for treatment at the OPD and IPD of the Department of Psychiatry fulfilling the following are included:

1. Patients with Post Schizophrenic Depression according to ICD10-DCR (International Classification of Diseases 10– Diagnostic Criteria for Research) (9).
2. Aged between 18 to 60 years of either sex
3. Patients with a positive score of less than 29 on the Positive and Negative Syndrome Scale (PANSS) (10)
4. Patients with a score of more than 6 on the Montgomery-Asberg Depression Rating Scale (MADRS) (11)
5. Patients without Extrapyramidal symptoms: a score of less than 3 on the Simpson-Angus Scale (12)
6. With Informed consent from the Legally Authorised Relative

EXCLUSION CRITERIA:

Patients with any one of the following are excluded from the study:

1. Patients with a medical or neurological disorder
2. Patients with a history of substance dependence
3. Patients with high suicidality
4. Patients with a past history of primary depression
5. Patients already on Olanzapine-Fluoxetine combination or Amisulpride

METHODOLOGY:

The proposed study would be an 8-week, randomised, controlled, parallel-group, clinical trial which will be conducted at the Inpatient and Outpatient settings of the Department of Psychiatry, AIIMS, Bhubaneswar. Patients with the diagnosis of Post Schizophrenic Depression according to the ICD 10 (DCR) and meeting all the Inclusion and Exclusion Criteria would be selected for the study. At first, the patients and their family members/ guardians would be explained about the study procedure along with its possible risks and benefits using a Patient Information Sheet (in their local language). After obtaining a written Informed Consent from the Legally Authorised Relative, the patients would be finally recruited for the study.

All recruited patients would be randomized using computer-generated random numbers into two treatment groups with an allocation ratio of 1:1. The sociodemographic and clinical data of the patients would be collected as per the designed sheets. Then at baseline, the CDSS and CGI ratings would be assessed, and the serum BDNF would be tested for each patient. The study would be rater-blinded. The experimental group would receive Amisulpride at a low dosage of 100-300 mg/day and the control group would receive a combination of Olanzapine at 5mg or 10 mg/day and Fluoxetine at 20mg/day.

The two groups would be followed for 8 weeks, at the completion of which all the patients would be reassessed. The follow-up assessment would involve a re-evaluation of the CDSS and the CGI scores and the Serum BDNF levels to see for any change. The data thus collected would be analysed, compared within and in between the study groups and statistical tests would be applied for drawing conclusions.

RANDOMIZATION:

All recruited patients will be randomized by computer-generated random number into two treatment groups with an allocation ratio of 1:1.

BLINDING:

The proposed study will be rater-blinded. The ratings of the CDSS and CGI scales would be done by a psychiatrist who would be blinded to the nature of the intervention provided.

FOLLOW UP:

All patients under the study will be followed for a period of 8 weeks from the start of the intervention. Then, the follow-up assessments will be done by rating the CDSS, and the CGI scales once again in each patient. Serum BDNF levels will be tested again. The data obtained will be compared within each group to find the change before and after the respective interventions. Thereafter, the magnitude of the changes will be compared in-between the groups to find out the efficacy and safety of one treatment over the other. All the results will be statistically tested to understand their significance.

OUTCOME MEASURES:

Primary Outcome Measure:

1. Calgary Depression Scale for Schizophrenia (CDSS) [Time Frame: 8 weeks]

Calgary Depression Scale for Schizophrenia (CDSS) (13) scores will be used to measure the change in the severity of depressive symptoms in the study groups from baseline over 8 weeks. the total score ranges from 0 - 36. Higher scores represent higher severity of depression.

Secondary Outcome Measures:

1. Clinical Global Impression (CGI) [Time Frame: 8 weeks]

Clinical Global Impression (CGI) scores (14) will be used to measure the change in illness severity, global functioning and improvement in the study groups from baseline over 8 weeks.

- The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale [minimum: 1 and maximum 7]: Higher scores means higher severity of disease.
- The Clinical Global Impression - Improvement scale (CGI-I) is a 7 point scale [minimum: 1 and maximum 7]: Higher scores means more clinical improvement.

2. Serum BDNF Levels [Time Frame: 8 weeks]

The change in serum BDNF levels in the study groups over 8 weeks.

3. Correlation [Time Frame: 8 week]

Determine the correlation (if any) between the between changes in CDSS scores, CGI scores and serum BDNF levels

4. Adverse Drug Reactions [Time Frame: 8 weeks]

Detect adverse drug reactions (if any) and grading their severity

STATISTICAL ANALYSIS PLAN:

1. The CDSS scores, the CGI scores and the serum levels of BDNF, being continuous variables would be expressed as a mean ± standard deviation (SD) / standard error of means (SEM)
2. The means would be compared within the group by two-sided paired t-test / Wilcoxon signed rank test
3. The means between the groups would be compared using unpaired t-test / Mann Whitney U test
4. Correlation analysis will be done between the CDSS ratings, the CGI scores and the serum BDNF levels.
5. The missing values would be replaced by the help of multiple imputations for conducting an Intention to Treat (ITT) analysis and the pooled data would be used for further analysis
6. All the statistical analyses would be performed using SPSS 23.0 (IBM, NY USA)
7. For obtaining statistically significant results, P value would be set at < 0.05

SAMPLE SIZE CALCULATION:

A sample size of 26 per group will achieve a power of 80%, to detect a difference of 3 in Calgary Depression Scale for Schizophrenia (CDSS) between the groups with known SD of 3.8 and with a significant level 0.05 using a Two-sided Two-sample T-test. Assuming attrition of 10-15% 30 patients in each group will be recruited.

Sample size calculation was done by PASS software (Version 11)

EXPECTED OUTCOME:

- The role of low dose Amisulpride in the treatment of Post Schizophrenic Depression can be explored for the first time (as no study has been done on it yet)
- Low dose Amisulpride is expected to be more efficacious than Olanzapine-Fluoxetine combinations in PSD. If this comes true, a new treatment strategy in PSD would be obtained.
- Use of Amisulpride in PSD would have the following advantages:
    1. Polypharmacy in PSD patients can be avoided
    2. Overall reduction in the medical expenditure of the patients
    3. Duration of treatment would not be an issue as in the case of treatments with antidepressants
    4. In advent of positive symptoms simply hiking the Amisulpride doses to higher dose range can treat the patients, without switching to any other antipsychotic.
    5. Lesser risk of side-effects in the patients, as Amisulpride is a relatively safer drug among other antipsychotics

ETHICAL ISSUES:

1. All works under the proposed study would begin only after obtaining approval from the Institutional Ethics Committee, AIIMS Bhubaneswar
2. All the patients and their family members/ guardians would be adequately explained, in the language they understand, about the study procedure and the possible risks and benefits associated with it. Only those patients with a written Informed Consent from the Legally Authorised Relative would be enrolled for the study.
3. Strict confidentiality would be maintained about the identity, sensitive information and personal details of the patients obtained during the course of the study.
4. Any patient can willfully withdraw his/ her participation at any point during the course of the study.
5. No bias in treatment and care would be done on any patient refusing to participate or withdrawing anytime from the study.
6. The efficacy and safety of all the medications and interventions used in the study have already been scientifically established
7. Standard treatment and care would be provided, within the limits of the institutional facilities, in cases of any adverse reaction arising due to the interventions.
8. The Patient Information Sheet would be provided with the contact details of the principal investigator and the guide so that the patient/ family member can contact anytime for any query regarding the study.

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PARTICIPANT INFORMATION SHEET

TITLE: EFFICACY AND SAFETY OF LOW DOSE AMISULPRIDE VS OLANZAPINE-FLUOXETINE COMBINATION IN THE TREATMENT OF POST SCHIZOPHRENIC DEPRESSION: A RANDOMIZED CONTROLLED TRIAL

Name: _____ Age/Sex: _____
LAR: _____ Contact No.: _____
Address: _____

Your patient is invited to take part in this research study. The information in this document is meant to help you decide whether or not he/she takes part. Please feel free to ask if you have any queries or concerns.

PURPOSE: Depression is common in the kind of mental illness (Schizophrenia) your patient is diagnosed with. So, along with the primary drug (Olanzapine), another drug (Fluoxetine, an antidepressant) is usually added to treat the depression. But no guidelines are available regarding the dose and duration of this second drug. Also, it adds to the overall costs of the medicines.

However, there is yet another drug (Amisulpride) used in this mental illness, which at lower doses is seen to treat depression effectively. In this study, we want to use this drug alone in one half of the patients and compare the response rates.

PROCEDURE: Your patient, if participates in this study will receive either the older two-drug combination (olanzapine and fluoxetine) or the other drug (Amisulpride). Then he/she will be followed for a period of 2 months for seeing the results of the treatment.
You are also informed that:

1. Both the treatments have established safety and efficacy. In case of any side-effect your patient will be adequately treated at our hospital, within the limits of its facilities.
2. The participation in this study is entirely voluntary.
3. Whether you participate or not, all the services in this hospital will continue and nothing will change.
4. You may change your mind later and stop your participation even if you agreed earlier.
5. If you have any questions, you can contact me directly or on my phone before, during or after the study.
6. This proposal has been reviewed and approved by the AIIMS ethical committee, which is a committee whose task is to make sure that research participants are protected from harm.
7. Your name will be confidential and your particulars will not be disclosed under any circumstances to anyone other than the individuals involved in the study.

PI:
Dr. Biswa Ranjan Mishra
Dept. of Psychiatry,
AIIMS, Bhubaneswar
Phone: 9438884220
Email: brm1678@gmail.com

PARTICIPANT INFORMED CONSENT FORM

Study No. _____
Participant identification number for this study: _____

TITLE: EFFICACY AND SAFETY OF LOW DOSE AMISULPRIDE VS OLANZAPINE-FLUOXETINE COMBINATION IN THE TREATMENT OF POST SCIZOPHRENIC DEPRESSION: A RANDOMIZED CONTROLLED TRIAL

PI: Dr. Biswa Ranjan Mishra Tel. No(s) 9438884220

I, _____, parent/legal guardian of _____, am authorized to give consent on behalf of _____ to take part in the above mentioned study.

The contents of the information sheet dated _____ that was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in details. I understand that the participation (of my patient) is voluntary and that I am free to withdraw at any time, without giving any reason, without my patient's medical care or legal right being affected. The institution will treat any treatment emergent adverse effect as per the standard guidelines.

I understand that the information collected about my patient from his/her participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS, Bhubaneswar. I give permission for these individuals to have access to his/her records.

I provide consent that my patient will be taking part in the above study.

_____ Date:
(Signatures / Left Thumb Impression) Place:

Name of the LAR: _____
Son / Daughter / Spouse of: _____
Complete postal address: _____
This is to certify that the above consent has been obtained in my presence.

_____
Signatures of the Principal Investigator Date: Place:

1) Witness – 1

_____
Signatures
Name:
Address:

2) Witness – 2

_____
Signatures
Name:
Address: