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Protocol

Safety and efficacy of Placida® (fixed dose combination of flupentixol 0.5 mg and melitracen 10 mg) in comparison to escitalopram 10 mg and clonazepam 0.5 mg in patients with comorbid anxiety and depression: a randomized, double blind, double dummy, parallel group clinical trial

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ABSTRACT

Background: Individuals with major depressive disorder (MDD) commonly present with comorbid anxiety and have greater depressive illness severity and chronicity, more suicide attempts, and completions. This randomized, double blind, double dummy, parallel-group clinical phase IV trial (CTRI/2022/11/047050) is aimed to compare the safety and efficacy of Placida® (FDC of flupentixol 0.5 mg + melitracen 10 mg) versus escitalopram + clonazepam in patients with comorbid anxiety and depression.
Methods: This is a randomized, controlled, double blind, double dummy, parallel-group, phase IV trial. A total of 440 patients was enrolled across 11 sites in India who fulfilled the inclusion and exclusion criteria. All the subjects will be followed up for 2, 4, 6, 8, 10, 12, 16, 20, and 24 weeks with a buffer period of 1 week in each visit. The patient will be checked for severity of adverse events (AEs) and serious adverse events (SAEs). Efficacy will be assessed using the Hamilton depression rating scale (HAM-D), Hamilton anxiety rating scale (HAM-A) at baseline, weeks 4, 8 and 16, 24 score-reduction rate from baseline to end of treatment and extrapyramidal symptom rating scale (ESRS) at week 16 and end of the study. The first enrolment was done on 26 November 2022 and presently the subjects are under follow-up stage. The anticipated completion date for the study is March 2024.
Conclusions: Outcomes of this trial will provide valuable information on safety and efficacy of Placida® as compared to escitalopram and clonazepam in treating patients with comorbid anxiety and depression.
Trial Registration: The trial is registered with clinical trial registry India (CTRI/2022/11/047050) prospectively.

Keywords: Anxiety, Flupentixol, Melitracen, Escitalopram, Clonazepam, Depression

INTRODUCTION

Depression and anxiety co-occur in more than 50% of individuals and are common symptoms in patients with chronic illnesses such as neurological diseases, hypertension, diabetes, gastro-esophageal reflux disease, functional dyspepsia and chronic bronchitis.[1-3] The comorbidity of anxiety and depressive disorders is commonly unrecognized and untreated as a result of which it may lead to worsening of somatic symptoms as well as weakened compliance with medication.[4-6] These symptoms can be relieved with timely identification and management and outcomes for better health can be targeted.[7] In India, the National Mental Health Survey 2015-16 revealed that nearly 15% of Indian adults need active intervention for one or more mental health issues and one in 20 Indians suffers from depression. Depression is characterized by a typically chronic course with associated anxiety symptoms as co-morbidity.[8,9] Associated anxiety symptoms may result in greater

symptom severity, higher suicidal risk, and poor treatment response than either depression or anxiety alone.[10] A significant overlap exists in the pathophysiologic components of depression and anxiety involving serotonergic, noradrenergic, and GABAergic systems in the brain and their treatment.[11] The selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) are reported to be effective in treating anxiety disorders associated with MDD.[11-13]

Escitalopram, a SSRI is approved for MDD and GAD in adults and children over 12 years of age. Clonazepam is a SNRI FDA-approved in the United States as a generic drug in 1997 used to prevent and treat seizures, panic disorder, anxiety disorders, and the movement disorder known as akathisia. In 2020, it was the 44th-most commonly prescribed medication in the United States, with more than 14 million prescriptions.[14] In many areas of the world, it is commonly used as a recreational drug.[15,16] Flupentixol is not approved for marketing in the United States by the U.S. Food and Drug Administration. It is, however, approved for use in the UK, Australia, Canada, Russian Federation, South Africa, New Zealand, Philippines, Iran, Germany, Islamic State, and various other countries.[17-19] Melitracen is a tricyclic antidepressant (TCA), for the treatment of depression and anxiety.[20-22] Head-to-head comparison of the fixed dose combination of flupentixol+melitracen and escitalopram+clonazepam drugs in the general population is lacking. Reviews and systematic analyses on SSRIs and SNRIs have conflicting results. Therefore, this study was undertaken to evaluate the clinical effectiveness and safety of Placida® [fixed dose combination of flupentixol 0.5 mg + melitracen 10 mg] in comparison to escitalopram 10 mg + clonazepam 0.5 mg in patients with comorbid anxiety and depression.

METHODS

Study design and setting

This is a multi-centre, randomized, double-blind, double dummy, parallel-group study to evaluate the safety and efficacy of fixed dose combination of flupentixol 0.5 mg + melitracen 10 mg in comparison to escitalopram 10 mg + clonazepam 0.5 mg in patients with comorbid anxiety and depression. This clinical phase IV trial is going in 11 sites in India after obtaining approval from all the respective institutional ethics committees. The trial is registered with clinical trial registry India (CTRI/2022/11/047050) prospectively. The study duration is approximately 24 months and the patient participation in the study is approximately six months.

Participants

A total of 440 patients were enrolled over a period of approximately six to eight months based on below mentioned inclusion and exclusion criteria.

Inclusion criteria

Eligible subjects were adults of age 18 years and 65 years and of either sex who were suffering from mild to moderate comorbid anxiety and depression according to ICD-10 criteria and prescribed either combination of escitalopram and clonazepam or Placida®; patients who do not have life-threatening, severe, or unstable disease/disorders or major cognitive deficits at baseline were enrolled; and women of childbearing potential having a negative urine pregnancy test, are not nursing, and are willing to use acceptable methods of contraception throughout the study period and patients who provided written informed consent prior to study initiation were included in the study.

Exclusion criteria

Patients with strong suicidal tendencies; patients with severe mental illnesses that could confuse assessment of depression and anxiety with severe anxiety and depression; patients with HAM-A score >25 and HAM-D score >19, participating in any clinical trial currently or within past 3 months; contraindications to the study drugs according to the prescribing information; treatment resistant to anxiety/depression; hypersensitivity to study drugs or to any of the excipients; patients with organic brain syndrome, convulsion, urinary retention, hyperthyroidism, advanced hepatic or cardiovascular disease and any other serious uncontrolled concomitant disease that would contraindicate the use of any drug used in this study or that would put the patient at high risk for study treatment-related complications; patients unable to comply with the protocol requirements; patients with continuing history of alcohol and/or drug abuse; patients taking a mono-amine oxidase inhibitor (MAOI), or within 14 days of discontinuing treatment with MAOI; and patients on other maintenance medications for anxiety/depression were excluded from the study.

Randomization

Patients fulfilling all inclusion and exclusion criteria's will be randomized for the treatment based on a computer-generated randomization. The block randomization schedule will be generated using SAS software (version: 9.4 or higher; SAS Institute Inc., USA). A unique randomization number will be assigned to each enrolled subject. Randomization will be stratified based on each study site (centre wise randomization). The randomized patient receives either test drug or comparator drug. The investigational products (IPs) viz. Placida® and escitalopram + clonazepam will be dispensed as per marketed labelling and packaging guidelines. Dummy IPs will be provided along with test and control drugs to facilitate double blinding in the study. Test drug, Placida® is an FDC of flupentixol + melitracen (0.5 mg + 10 mg) and control drug is FDC of escitalopram + clonazepam (10 mg + 0.5 mg).

Blinding and unblinding

This study will be conducted as double-blind, double dummy study. All study drugs will be supplied in identical packages. The dispensing of the study drug will be carried out by a qualified and trained pharmacist. The study blind will be broken only in case of medical emergencies where knowledge of the study drug received would affect the treatment of the emergency. The blind will be broken only after discussion on a case-by-case basis, at the discretion of the sponsor/medical monitor. If an emergency unblinding becomes necessary, the PI will notify the sponsor/medical monitor. The unblinded team members will not be involved with any other aspects of the study conduct except dispensing the study drug.

Screening and baseline assessments

The eligible patients will be included from outpatient or inpatient. Written informed consent for participation in the study will be obtained before performing any study-specific screening tests or evaluations. Screening tests and evaluations will be performed within 7 days prior to the first study medication administration unless otherwise specified. All screening evaluations will be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The HAM-A and HAM-D scale will be filled and below mentioned examinations will be performed during this baseline visit. All the data will be captured in case report form (CRF).

Demographic data will include age, sex, weight, and height.

Medical history includes clinically significant diseases, surgeries, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the subject within 28 days prior to the screening visit.

Vital signs include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, body temperature

Physical examinations include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline will be recorded on the medical history in CRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed and changes from baseline abnormalities will be recorded. New or worsened clinically significant abnormalities will be recorded as adverse events on the adverse event log in CRF.

Psychiatric history was assessed.

Laboratory Investigation includes hematology (red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] with differential count [neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells]), serum chemistry (sodium, potassium, blood glucose, creatinine, total bilirubin, alkaline phosphatase [ALP], alanine transaminase [ALT], aspartate aminotransferase [AST], uric acid, thyroid function test – T3, T4, TSH. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. If the required baseline tests have been done within 7 days of screening, then above tests will not be repeated.

After the randomization, patients will receive either escitalopram (10 mg) and clonazepam (0.5 mg) one tablet once daily at bedtime for a period of 24 weeks, or FDC of flupentixol 0.5 mg (as 0.584 mg flupentixol dihydrochloride) plus melitracen 10 mg (as 11.25 mg melitracen hydrochloride) 2 tablets daily: morning and noon in the 1st week followed by a single tablet thereafter for 24 weeks. An identical placebo for comparator drugs will be administered twice daily for the 21 weeks followed by a single tablet thereafter for 24 weeks in the evening. An identical Placebo for test drugs will be administered twice daily for 21 weeks followed by a single tablet thereafter for 24 weeks in the morning (Tables 1 and 2).

Table 1: Treatment for 1st week.

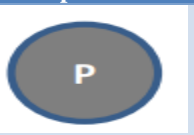
Time	Placida® arm	Escitalopram + clonazepam arm
Morning	 Placida® *(drug)*	 Placida® *(placebo)*
Noon	 Placida® *(drug)*	 Placida® *(placebo)*
Evening	 Escit + clonazepam *(placebo)*	 Escit + clonazepam *(drug)*

Accountability

The medication prescribed will be recorded in the CRF of patients. The dose of the IPs dispensed to each subject will not be given for more than 2 weeks until 12 weeks and IPs will be dispensed monthly basis thereafter. Family members for any non-compliance will supervise the intake of the medication. The patients will be interviewed for compliance to the study medication at subsequent follow-up visits and same will be recorded. At each visit, the subject will be instructed to bring remaining IPs/container

in his/her possession for reconciliation by the treating physician/investigator.

Table 2: Protocol for beyond week 1.

Time	Placida® arm	Escitalopram + clonazepam arm
Morning	 Placida® *(drug)*	 Placida® *(placebo)*
Evening	 Escit + clonazepam *(placebo)*	 Escit + clonazepam *(drug)*

Follow-up

Patients will receive study medication at baseline after randomization for a minimum of 16 weeks or maximum of 24 weeks till investigator's discretion whichever comes first, or until unacceptable AE as determined by the Investigator, or withdrawal of consent. All the subjects will be followed up for 2, 4, 6, 8, 10, 12, 16, 20, and 24 weeks with a buffer period of 1 week in each visit. The patient will be checked for severity of adverse events (AEs) and serious adverse events (SAEs) and recorded in the log of respective CRF. The primary outcome will be measured as the incidence and severity of adverse events (AEs) and incidence of serious adverse events (SAEs) up to 24 weeks. The secondary outcome measures will be changes from baseline to study end of HAM-A at week, 4, 8, and 16, HAM-D scores at week 4, 8, and 16. Score-reducing rate for HAM-A and HAM-D scores (defined as percent reduction in HAM-A and HAM-D scores) from baseline to end of Treatment. Compliance for treatment, extrapyramidal symptom rating scale (ESRS) questionnaire for Placida®, a fixed-dose combination of flupentixol and melitracen (0.5 mg and 10 mg) in comparison to escitalopram and clonazepam (10 mg and 0.5 mg) at week 16, and end of the study. In addition, compliance to prescribed medication will be checked at each follow-up visit. At each visit, the patients will be asked about their medication intake, the IPs in their possession will be reconciled. Abstinence of seven consecutive days will be considered as therapy non-compliance.

Final study visit

This visit will be conducted at week 24. The patients enrolled will be followed up until treatment continues or up to 24 weeks, whichever is earlier. The final data regarding any AE/SAE will be recorded along with compliance to prescribed medicine 4-weeks after completion of treatment or 24-weeks whichever is earlier.

Pregnancy visit

If a subject becomes pregnant during the study duration, she will be discontinued from the study. All data collected till that time will be a part of analysis. Pregnancy will be considered as a medical event and not as an AE/SAE and will be recorded appropriately in the CRF.

Unscheduled visits

In case of any adverse event or as per the physician's decision there may an unscheduled visit planned for any subject. The details in any such event will be captured in the CRF.

End of study visit

The patients will be followed up for 4 weeks for any withdrawal symptoms after the end of treatment. The patients for whom the end of treatment will be week 24, their end of study visit will be week 28±1 weeks.

Statistical analysis

Demographic and baseline characteristics will be summarized based on modified intention-to-treat (mITT), per protocol (PP), and safety populations. Frequency and percentage of patients will be presented for age category, gender, height, and weight. Age, height, and weight will also be summarized as a continuous variable. Descriptive summaries will be provided for observed and change from baseline by visit for HAMD and HAM-A score. The primary analysis for the efficacy end points will be based on the mITT population. The change from baseline in HAM-D and HAM-A scores (efficacy endpoints) at weeks 4, 8 and 16 will be analyzed using analysis of covariance (ANCOVA) model with treatment as factor and baseline scores as covariate.

A score-reducing rate, expressed as (pre-treatment score of HAM-D/HAM-A – after-treatment score of HAM-D/ HAM-A)/ pre-treatment score of HAM-D/HAM-A, will be used to evaluate the treatment effect. The criteria of curative effect based on score-reducing rate will be as follows: recovery ≥75%, significant improvement =50~75%, improvement=25% ~ 49% and ineffectiveness <25%.

Separate analysis will be conducted for HAM-D and HAM-A scores. Comparison between flupentixol + melitracen (0.5 mg+10 mg) versus escitalopram + clonazepam (10 mg + 0.5 mg) will be made using the difference in least-square estimates and p values from the ANCOVA model. Non-inferiority will be concluded at a one-sided alpha level of 0.025 if the lower limit of the corresponding two-sided 95% confidence interval for this treatment difference is greater than or equal to non-inferiority margin of -2.5. The analysis for the efficacy endpoints will be conducted using mITT and PP populations.

The first enrolment was done on 26 November 2022 and the subjects are under follow-up. The anticipated completion date for the study is March 2024.

DISCUSSION

Depression is a chronic disease characterized by recurrent episodes that interfere with daily life and normal functioning, imposing large costs for patients as well as society. Indeed, depression and other mental illnesses result in a greater loss of healthy life years to disability and death than cardiovascular disease, cancer, or diabetes.[23] The onset of mental illness occurs primarily at a young age—by age in 75 percent of cases - but can strike at any age.[24,25] Regardless of age at onset, a study by the Council of Medical Directors of the National Association of State Mental Health Program Directors showed that individuals who received treatment for a serious mental illness still die 25 years earlier than the normal population.[25] Disconcertingly, similar statistics are not available for those who do not receive the care for a mental illness. The neuroscience knowledge base underlying the study of depression has been growing since the emergence of biochemical pharmacology and molecular technologies in the 1970s and 1980s. Over this same period, pharmaceutical companies, the National Institutes of Health's (NIH's) National Institute of Mental Health (NIMH), and patient advocacy groups have aggressively pursued new treatments for the disease. The success of selective serotonin reuptake inhibitors (SSRIs) and the many structurally similar drugs that followed improved the lives of many patients. According to Potter, the period of SSRI development established a level of comfort in the mental health community that may have temporarily hindered the development of new and better antidepressants. Today, significant effort is focused on understanding the challenges of developing novel antidepressant therapies and designing the informative clinical trials necessary to test the effectiveness of new discoveries.

SSRIs may affect the concentration of essential neurotransmitter substances in the brain and are therefore considered to exert effects on depressive symptoms. However, whether these effects are beneficial and clinically meaningful is the question. Estimating a meaningful threshold for clinical significance is difficult and an assessment of clinical significance should ideally not include a threshold on an assessment scale.[26] Major depressive disorder affects daily functioning, increases the risk of suicidal behaviour, and decreases the quality of life.[27] Some adverse events might therefore be acceptable if SSRIs have clinically significant beneficial effects.[27-29]

The IPS multicentric study in 2013 evaluated the prescription pattern for antidepressants by psychiatrists for the treatment of first-episode depression.[30] According to this study; escitalopram was the most commonly prescribed antidepressant, comprising 40% of the total prescriptions. On the other hand, the escitalopram group reported restlessness, erectile dysfunction, and loss of libido as the main adverse effects.[31] Erectile dysfunction and loss of libido were experienced by the patients till the end of the study. Sexual functioning is an important aspect of the quality of life. In the literature, some evidence suggests a range of 25%–75% prevalence of sexual dysfunction caused due to SSRI others suggest that the exact prevalence is not well characterized due to underreporting on the part of the patient due to noncompliance and dropping out of the treatment and factors such as gender bias, lack of sex education, and cultural norms resulting in an underreporting of sexual side effects in general.[32,33] Therefore, it can be inferred that escitalopram was better tolerated than venlafaxine, but sexual side effects were seen more commonly in the escitalopram group. Whereas clonazepam's long half-life and high potency profile is a major clinical concern because withdrawal symptoms can both appear and last for months after the drug is stopped, a phenomenon that would only be evident in a longer-term study. Muscular relaxation is one of the important side effects of clonazepam. Flupentixol is an antipsychotic drug of the thioxanthene group. It exists in two geometric isomers, the trans(E) and pharmacologically active cis(Z) forms. Flupentixol decanoate is one of the active ingredients found in injectable drug formulations. Flupentixol is an antagonist of both D1 and D2 dopamine receptors.[34] It is used for the management of chronic schizophrenia in patients whose main manifestations do not include excitement, agitation or hyperactivity.[35] It has been marketed to manage symptoms of depression in patients who may or may not exhibit signs of anxiety.[36] In combination with melitracen, flupentixol is used to manage symptoms of anxiety, depression, and asthenia.[37] Whereas melitracen is a thioxanthene neuroleptic, tricyclic antidepressant indicated in the treatment of anxiety, depression, and asthenia. It increases the levels of chemical messengers in the brain that help in regulating the mood and treat depression.[38,39] In the present clinical trial, the combination of the two compounds (Placida®) [flupentixol + melitracen (0.5 mg+10 mg)] was designed to enhance the pharmacological effects as well as to lower the AEs and SAEs incidents compared to escitalopram and clonazepam.

CONCLUSION

This study has been designed to assess, primarily, safety and efficacy of a fixed-dose combination of Placida® [flupentixol + melitracen (0.5 mg+10 mg)] in India. This study will help to gain more information regarding safety of this combination in patients with comorbid anxiety and depression. Additionally, a comparative evaluation of efficacy with escitalopram + clonazepam (10 mg + 0.5 mg) from baseline towards end of the treatment was carried out. There is lack of data in Indian population on use of the combination regimen of flupentixol + melitracen (0.5 mg+10 mg) which is commonly used for low level anxiety, depression, and similar disorders.

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