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Protocol

Safety and effectiveness of fixed dose combination of amitriptyline and chlordiazepoxide (Libotryp® and Libotryp-DS®) in the management of depression with co-morbid anxiety: protocol and design of a prospective, single arm, multi-centric, PMS study

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ABSTRACT

Background: Depression and anxiety are most disabling psychiatric conditions and add significantly to global health-related burden. Lifetime prevalence of major depression and anxiety disorders are very common and many times they can co-exist in the same time frame. The outcomes are poorer in such situations and compliance to medication is key to improve prognosis. A combination of tricyclic antidepressants and benzodiazepine is more practical in terms of compliance, and advantageous than that of a single class of drugs for the management of depression with co-morbid anxiety. This study will evaluate the safety and effectiveness of a fixed dose combination of amitriptyline and chlordiazepoxide as a part of post marketing surveillance.
Methods: This is a prospective, single-arm, multi-centre, study which enrols patients who have been initiated with FDC of amitriptyline and chlordiazepoxide (Libotryp®: amitriptyline 12.5 mg and chlordiazepoxide 5 mg or libotryp-DS®: amitriptyline 25 mg and chlordiazepoxide 10 mg) tablets for the treatment of depression with co-morbid anxiety. A total of 375 patients will be enrolled and clinical assessments for safety will be done at follow up visits; assessments for effectiveness will be done using Hamilton Depression Rating Scale (HDRS or HAM-D) and Hamilton Anxiety Rating Scale (HARS or HAM-A).
Conclusions: This study will provide more evidence on safety and usefulness of FDC of amitriptyline and chlordiazepoxide for the treatment of depression with co-morbid anxiety from Indian context.
Trial registration: Trial registration number is CTRI/2021/03/031971.

Keywords: Depression, Anxiety, Fixed dose combination, Amitriptyline, Chlordiazepoxide

INTRODUCTION

Psychiatric disorders add significantly to the global health-related burden, and the most disabling conditions among these are depression and anxiety, the global burden of diseases, injuries, and risk factors study (GBD) 2019).[1] Lifetime prevalence of anxiety disorders and major depression among adults as per National Comorbidity Survey Replication study in United States has been reported to be 28.8% and 16.6%, respectively.[2] As per GBD Study (1990-2017) in India, 197.3 million people had mental disorders, including 45.7 million with depressive disorders and 44.9 million with anxiety disorders.[3] Depression and anxiety have a bidirectional relationship and can frequently co-occur during the same time frame.[4] With respect to major depression, a

worldwide survey reported that 45.7% of individuals with lifetime major depressive disorder had a lifetime history of one or more anxiety disorder.[5] Data from the well-known sequenced treatment alternatives to relieve depression study demonstrated comorbidity at the symptom level, as 53% of the patients with major depression had significant anxiety and were considered to have an anxious depression.[6] In a study conducted in Southern India it was found that about 87% patients of depression were also suffering from anxiety disorder.[7] Depression with co-morbid anxiety has a poorer prognosis than either disorder alone and the outcomes largely depend on the quality of compliance to treatment.[8,9] Amitriptyline, a tricyclic antidepressant (TCA), is approved for the management of major depressive disorder (MDD), and chlordiazepoxide is a long-acting benzodiazepine and is indicated in the treatment of mild-moderate to severe anxiety, pre-operative anxiety, and alcohol withdrawal. Like other medications in the benzodiazepine class, it serves as an augmenting agent to antipsychotics, mood stabilizers, selective serotonin reuptake inhibitors (SSRI) and serotonin and norepinephrine reuptake inhibitors (SNRI) to treat psychotic, bipolar and anxiety disorders.[10] It is one of the least harmful of the effective psychopharmacological benzodiazepines.

Mood disorders such as anxiety and depression impair cognitive function, motivation, and ability to follow through with treatment.[11] Depressed patients are 3 times as likely as non-depressed patients to be noncompliant.[11] Combination products reduce the number of medications to be taken, improve compliance and provide benefits like maximizing therapeutic efficacy, but at the same time may have potential to augment side effects.[12,13] The combination of amitriptyline and chlordiazepoxide is more practical and advantageous than that of a single drug in depression with co-morbid anxiety, and is already approved in United States.[14] This study will evaluate the safety and effectiveness of a fixed dose combination (FDC) of amitriptyline and chlordiazepoxide in Indian patients as a part of post marketing surveillance (PMS).[15]

METHODS

Recruitment and study design

This is a prospective, single arm, multi-centric PMS study performed in patients of depression with co-morbid anxiety, prescribed with FDC of amitriptyline and chlordiazepoxide tablets (Libotryp®: amitriptyline 12.5mg and Chlordiazepoxide 5mg or Libotryp-DS®: amitriptyline 25 mg and chlordiazepoxide 10 mg) with a follow up period of 2 months. The design of the study is depicted in (Figure 1). The study has been registered with CTRI (Regd. No. CTRI/2021/03/031971) and will be conducted from August 2022 till March 2023. During the first visit i.e., day 0, full details of the study will be provided, and participants will be invited to participate in the study.

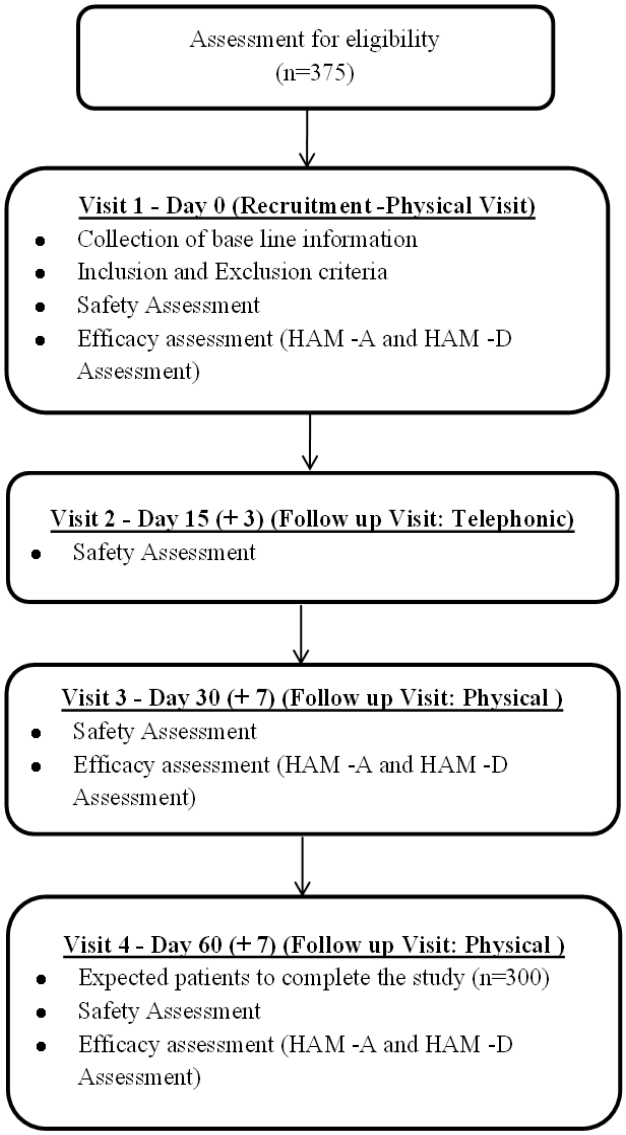

Figure 1: Design of the study.

A signed consent will be obtained from all eligible patients. The general data such as demographics (age and gender), concomitant illness, psychiatric symptoms, complete details of present medication will be collected. Pulse rate, blood pressure, respiratory rate and electrocardiogram (ECG) details (if done) by investigator will be recorded. Drugs taken by the patient for any pre-existing and underlying medical conditions will be documented as concomitant drugs. This data collected during first visit will be considered as base line data. The patients will be followed up on visit 2 i.e., day 15 (telephonic/optional), visit 3 i.e., day 30 (physical) and visit 4 i.e., day 60 (physical) end of the study visit. Acute psychopathology will be assessed during visit 1, visit 3 and visit 4. Patients will be actively assessed for drug safety on all visits and are encouraged to report adverse events (AE). On day 0, 30 and day 60, patients will have

psychiatric evaluation to measure the effectiveness of treatment for depression and anxiety separately. On day 30 and day 60, patients will be assessed for change of treatment, concomitant medication (if any). All assessment details at every visit will be recorded in a Surveillance Record Form (SRF).

Sample size

Considering incidence rate of 0.01, expected events as 2 and a power of 80%, a sample size of 300 is required.[16] Anticipating a 20% dropout rate, a total of 375 participants will be recruited from 5 to 8 investigators across India.

Inclusion criteria

For inclusion in the study, patients must meet all the following criteria: age: ≥18 years old, both males and females will be included, patients with depression with co-morbid anxiety who experience at least a moderate level of depression and anxiety symptoms based on HAM-D and HAM-A respectively, and newly prescribed with FDC of amitriptyline and chlordiazepoxide (Libotryp®: amitriptyline 12.5 mg and chlordiazepoxide 5 mg or Libotryp-DS®: amitriptyline 25 mg and chlordiazepoxide 10 mg) tablets as per clinician's discretion, the subject must give free and informed consent, and sign the consent form.

Withdrawal criteria

The participants can be withdrawn from the therapy on account of development of an intolerable AE or if the physician feels that further continuation on surveillance drug will adversely affect the patient. A participant can also be withdrawn in case if he/she volunteers to do so. For any withdrawal from this study, investigators must keep a record of withdrawal reason in the SRF. In case of patients who withdraw due to AE, the investigators should closely follow up them until the AE disappear, return to the baseline state or the AE condition is stable. Patients who prematurely discontinue before day 60 visit will be analysed using their day 30 data and for those who discontinue before day 30 visit will be analysed only for safety and not for effectiveness.

Assessment and collection of outcomes

All investigators will be trained on protocol and related updates. The data of each participant will be recorded into the SRF carefully and will be reviewed by the investigators. Each SRF (with or without an AE) will be assessed by medical personnel after data entry, coding, and quality review.

Patient confidentiality

Patient names will be kept confidential. Patient will be informed that regulatory authorities may inspect their records and the personal information made available for inspection will be in accordance with local data protection laws and handled in confidence. Each participant will be issued a unique 03 digit number during visit 1. The first is the site code and next two are sequential number. Sites will be coded as A, B, C and so on. Order of patients screened at those sites are read as 01, 02, 03 etc., Unique ID will be written on the SRF. The participants confidentiality will be maintained before, during and after the study.

Safety assessment

Safety assessment is the primary objective of this study and will be done with a focus on sedative effects (drowsiness, somnolence), anticholinergic side effects (dry mouth, constipation, blurring of vision, tachycardia, urinary retention), dizziness, decrease in libido or any other adverse drug reactions (ADR). Patients will also be encouraged to report AEs (if any) throughout the study period. Details of the drugs administered for the treatment of AE will also be documented in the SRF. The grading of the severity of the AE will be as per common terminology criteria for AE Common Terminology Criteria for Adverse Events (CTCAE) (v5).[17] The causality assessment of AE with FDC of Amitriptyline and Chlordiazepoxide will be done as per WHO-UMC causality assessment system.[18] Serious, life-threatening, or unexpected AE, regardless of causality or relationship to drug, will be reported immediately (but not later than 24 hours). In case of serious AE, suspected unexpected serious adverse reaction (SUSAR) and events of pregnancy additional follow-up information will be requested from the prescribing physician. The collected data will be reviewed for safety and tolerability related assessment. All AE will be analysed with respect to incidence, causality, seriousness, severity, expectedness, and outcome.

Assessment of effectiveness

Patients will be assessed for effectiveness of treatment using Hamilton Depression Rating Scale (HDRS or HAM-D) and Hamilton Anxiety Rating Scale (HARS or HAM-A) to study depression and anxiety levels respectively and license has been obtained for use of the scales from respective license holders. The end points for effectiveness are the proportion of patients showing at least 50% decrease in baseline HAM-D and HAM-A scores at end of 30 days and 60 days of therapy. HAM-D scoring is based on 17 items and generally takes 15-20 minutes to complete the interview and score the results. Items are scored on a 3, 5-point scale, ranging from 0=not present to 4=severe. A HAM-D score of 0-7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial. HAM-A consists of 14-symptom defined elements and each item is scored on a basic numeric

scoring of 0=not present to 4=severe. A score of <17 is taken to indicate mild anxiety, 18-24 mild to moderate severity, 25-30 moderate to severe and higher scores indicates more severe disease.[19,20]

Statistical analysis

The data from all sites will be pooled together for analysis. The demographic, baseline and follow up data will be presented by appropriate descriptive statistic methods. Effectiveness of the study drugs will be assessed as per scoring captured by HAM-A and HAM-D analysis and patients showing 50% decrease in the score will be considered as improved. All the collected data will be analysed using appropriate statistical tests and a $p<0.05$ will be considered as significant. Patients who prematurely discontinue before day 60 visit will be analysed using their day 30 data. The participants who discontinue before day 30 visit will be analysed only for safety, and not for effectiveness.

DISCUSSION

The presence of comorbid anxiety with psychiatric disorders, generally predicts worse outcomes, more significantly when it co-occurs with depression. Although some anti-depressants have anxiolytic properties, addition of a specific anti-anxiety agent is required to achieve appropriate therapeutic outcome.

Chlordiazepoxide is primarily an anxiolytic and may improve mild depressive symptoms secondarily due to lessening of tension and anxiety, and consequent elevation of mood. Amitriptyline is primarily an antidepressant with anti-anxiety properties and is effective in both endogenous and neurotic depression. Due to its weak calming effect, it has been tried in combination with an anti-anxiety agent like chlordiazepoxide and found very useful. Both drugs are widely used in clinical practice and are considered quite safe. Addition of chlordiazepoxide extends and enhances the therapeutic benefits of amitriptyline in anxious depressed patients.[15,16,21]

This study provides more evidence on safety and usefulness of FDC of amitriptyline and chlordiazepoxide for the management of depression with co-morbid anxiety. The core aspects which make this study important and unique are active surveillance of ADR profile in a wider population providing information on safety especially when combining products with different mechanism of actions. AEs will be actively collected, recorded, reported, and assessed for both grading of severity and causality which will provide more understanding of AEs in relation to the study drug. The distribution of ADRs among the patients will be noted in terms of frequency, seriousness, causality and looked for any potentiation of drug effects for the combination. ADRs presumed due to the chlordiazepoxide component can be isolated instances of tension or excitement, whereas dry mouth, nausea, weakness, drowsiness, constipation, or nasal congestion can be due to amitriptyline.

Symptoms such as restlessness, tension, gastrointestinal upsets, and fatigue are often reported in psychiatric disorders which are not necessarily drug-related, will be considered side effects of medication only when not present at the beginning of the study.[15]

Evaluation of effectiveness further strengthens the evidence in terms of usefulness in a real time setting increasing the generalizability of the study results especially to a primary care practice.

HAM-D or HDRS, once considered to be the 'gold standard", is a widely used scale to measure the efficacy of antidepressant medication especially in clinical trials.[19,22] Though the internal, inter-rater and retest reliability estimates are weaker for individual items, they are adequate for the global score which is a good representative of overall effect.[23] HAM-A or HARS, one of the first rating scales to measure the severity of perceived anxiety symptoms, is still often used in clinical research trials (both of medication and psychological interventions).[24] The reliability and concurrent validity of the HAM-A and its subscales were sufficient to show that there is a reasonable inter-rater reliability and good one-week retest reliability.[25]

Evaluating both HAM-D and HAM-A provides information on sensitive changes in symptoms from baseline to end of study, considering strong re-test reliability both for depression and anxiety separately. This study will also provide additional information confirming the previous findings of other studies that chlordiazepoxide may not neutralize any of the therapeutic actions of Amitriptyline.[15,26,27] The study will provide substantial information for the safety and effectiveness of this fixed dose combination from Indian perspective.

CONCLUSION

The information provided by this study will add to the existing evidence of safety and effectiveness of FDC of Amitriptyline and Chlordiazepoxide for the management of depression with co-morbid anxiety, especially from Indian context.

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Conflict of interest: Dr. Sunil Kumar Yadav Y., Dr. Snehal Muchhala, Ms. Seema Bhagat, Dr. Rahul Rathod, Dr. Amey Mane, Dr. Bhavesh Kotak are employees at Dr. Reddys Laboratories. (Libotryp®: Amitriptyline 12.5 mg and Chlordiazepoxide 5 mg or Libotryp-DS®: Amitriptyline 25 mg and Chlordiazepoxide 10 mg) is a proprietary product of Dr. Reddy's Laboratories Limited.
Ethical approval: The study was approved by the Institutional Ethics Committee

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