PROTOCOL

Efficacy and Safety of Ayurveda Interventions for Depression: A Systematic Review Protocol

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ABSTRACT

Introduction: Depression is a disorder of major public health importance. The widely prescribed antidepressants of modern science are falling short in effectively managing the depression. Recent studies reported that depressive patients prefer to use other treatment options like complementary and alternative medicine (CAM therapies). Although systematic reviews on this topic have been published for CAM therapies; however, exclusive to Ayurveda interventions has not been performed till date. Therefore, the present study is intended to do a systematic review of the published clinical data in view of safety, efficacy, or effectiveness of Ayurvedic interventions in the management of depression and meta-analysis of eligible studies will be carried out, if appropriate.

Materials and methods: A systematic review of randomized controlled trials (RCTs), multiple arms clinical trials, trial quasi-experimental trials (nonrandomized controlled clinical trials and before after studies), and observational studies (case series and case reports) will be performed through databases like PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), DHARA, Google Scholar, and Online clinical trials registers. Studies published from the date of inception till the date the searches are run will be sought. The selection of the studies, data abstraction, and validations will be performed independently by the reviewers and any disagreements will be discussed by the team with fourth reviewer to reach consensus. Established guidelines for study selection, quality assessment, and presentation will be followed. Risk of bias assessment will be performed with the help of Cochrane risk of bias tool for randomized trials (RoB2) tool for RCTs and risk of bias tool to assess nonrandomized studies of interventions (ROBINS-I) tool for non-RCTs (NRCTs). Results of the study will be narratively synthesized and presented in count, percentage, and frequency and meta-analysis will be planned if they are sufficiently homogeneous. Patients will not be involved in any phase of the study; however, ethical approval has been obtained from the Institutional Ethics Committee.

Dissemination: The systematic review will be published in a peer-reviewed journal and will also be disseminated electronically and in print. The review may guide healthcare practices and policy framing regarding the treatment of depression with Ayurvedic interventions.

Study registration no: PROSPERO-CRD42020139382.

Keywords: Ayurveda, Depression, Kaphonnada, Systematic review, Systematic review protocol, Vishada.


INTRODUCTION

Depression is a mood disorder characterized by sadness, lack of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, undue feelings of tiredness, and poor concentration. It is a disorder of major public health importance, in terms of its prevalence and the suffering, dysfunction, morbidity, poor quality of life, economic burden, and most importantly higher risk of suicides. Being a common illness, more than 264 million people are affected worldwide with depression. Globally for all ages and both sexes, between 1990 and 2007, the number of all-age years lived with disability (YLDs) attributed to depressive disorders increased by 33.4% (31.0–35.8), becoming the third leading cause of all-age YLDs in 2007. It is estimated that by the year 2020 the burden of depression will increase to 5.7% of the total burden of disease and it would be the second leading cause of disability-adjusted life years (DALYs), second only to ischemic heart disease. It is projected to be the second leading cause of burden of disease by 2030 after human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). According to WHO, every year, 5.8% males and 9.5% females experience episodes of depression worldwide. As the burden of mental health conditions like depression is peaking globally, a World Health Assembly resolution was passed to call for a comprehensive, coordinated response to mental disorders at the country level in May 2013. And WHO’s mental health Gap Action Programme (mhGAP) has taken depression as one of the priority conditions to combat it globally.

Antidepressant medications are the most commonly used treatments for depression and ~35 different antidepressants in a number of classes are currently available worldwide. The widely prescribed antidepressants of modern science are falling short in effectively managing the depression and the choice of an antidepressant is largely influenced by its side effect profile. The most troubling adverse effects of the antidepressants are sexual dysfunction, weight gain, and sleep disturbance and they are the most frequent reasons cited by the patients for discontinuation.
of the medication. Treating depression in people with a chronic physical comorbidity is potentially more challenging in terms of these adverse effects of medication. Furthermore, it is reported that ~70% of patients with major depression do not achieve remission after initial pharmacological treatment. Moreover, treatment-resistant depressed patients may also not respond to standard treatment protocols, such as mindfulness-based cognitive therapy and cognitive behavioral therapy. Therefore, patients may wish to consider other treatment options like complementary and alternative medicine (CAM therapies). Recent studies reported that patients with severe depression prefer to use CAM therapies in addition to psychiatric services and those with moderate condition seem to use CAM therapies as alternative measures.

The realm of psychiatric diseases is described in Bhootavidya branch of Ashtanga Ayurveda and is dedicated to psychiatry. The major psychiatric illnesses are described under the umbrella term “Unmada” and depressive disorders can be compared to Kaphaja Unmada due to similarity in the symptomatology that is available in all classical texts of Ayurveda and it is observed that more than 70% of the symptoms of depressive disorders are present in Kaphomada. If we look into the symptoms of depressive disorders, we can find that similar presentation can be seen in Vishada also which is one of the Vataanatmaja Vikaras.

Ayurveda provides rational means for the treatment of many physical and mental disorders, which are considered to be obstinate and incurable in other systems of medicine, still keeping the criteria for prognosis. Ayurveda has long proposed a pathophysiological mechanism that is strikingly similar to a new biomedical understanding which links psychiatric illness to a dysregulation of the physical entities, especially in the gastrointestinal tract. The intricate and interdependent psychophysiological qualities to be health promotive or pathological are determined by the state of balance of Shareerika Doshas (bodily humors)/Manodoshas (humors of mind). And thus, three-fold treatment modalities, viz., Yuktivypasraya (treatment based on logic), Daivavyapasraya (spiritual therapy), and Satwawajaya (psychotherapy) find their role in Ayurvedic psychiatry too. Due to the variability in etiological factors, Dosa—Dusya vitiation and specificity of manifestation different treatment modalities like internal administration of medicine (either for Shodhana (bio-purification therapy) or Shamana (pacifying therapy)), external applications, surgical interventions, spiritual therapy, and psychotherapy are vividly mentioned in Ayurvedic classics.

Why it is Important to Perform this Review?

The world is witnessing a rollback to traditional, wholesome, and safe solutions in healthcare especially in psychiatry. Ayurvedic literature provides a wide variety of pharmacological and nonpharmacological treatment modalities and is in practice for depressive disorders from eons. Various clinical trials have also been conducted, but are lacking an organized evidence-based data generation through extensive systematic review. In the hierarchy of pyramid of evidence, the systematic review and meta-analysis are placed at the highest level. In the case of depression, many systematic reviews and meta-analyses have been published in light of modern regimens. Though some systematic reviews are also available for CAM therapies; however, exclusive to Ayurveda interventions has not been performed till date. Therefore, it is intended to do a systematic review of published clinical trials of Ayurvedic interventions in the management of depression and meta-analysis of eligible studies will be carried out, if appropriate.

This study reviews clinical trials on Ayurveda management of depression to generate evidence on their safety and efficacy. The importance of this review is to highlight the advantages of Ayurvedic interventions in depression along with their safety and efficacy, to develop practice guidelines, and to provide relevant information for future research efforts including knowledge gap to the stakeholders in the global arena.

**Review Question**

This review seeks to establish, through the available literature, the effectiveness of Ayurveda intervention in the management of depression. The specific review question to be addressed is:

“Are Ayurvedic interventions are effective and safe as standalone or adjunctive therapy in the management of depression?“.

**Objectives**

- Systematic review of the published clinical data in view of safety, efficacy, or effectiveness of Ayurvedic interventions in the management of depression.
- Meta-analysis of the published clinical data in view of clinical safety and efficacy or effectiveness of Ayurvedic interventions in the management of depression (will be carried out as appropriate depending on the availability of sufficient data of eligible studies).

**Materials and Methods**

This review protocol has followed the PRISMA protocols guidelines and Cochrane Handbook for Systematic Reviews of Interventions for its structure and organization. Furthermore, the consolidated standards of reporting trials, and the guidance on the conduct of narrative synthesis in systematic reviews will also be used as applicable.

Patients will not be involved in any phase of the study. Ethical approval has been obtained from the IEC of CARICD (1-12/2015-ACRI/Tech/IEC/Part-II dated 16.07.2019).

**Criteria for Selection of Study**

**Types of Participants/Population**

Studies of participants diagnosed with depression using standard criteria of modern medicine and/or Ayurvedic symptomatology for Kaphomada or Vishada of age 18 and older will be selected.

**Types of Interventions**

Any Ayurvedic intervention or combination of Ayurvedic interventions or Ayurvedic intervention as an adjuvant to conventional treatment given for the treatment of depression, including (but not restricted to) Shodhana, Panchakarma, Deepana, Pachana, Shamana, Satwawajaya, and Rasayana with any dose, type, schedule, medicine form, and Pathyapathy.

**Comparators/Control**

Ayurveda treatment (Shamana or/and Shodhana) with different dose, type, schedule, medicine, medicine form as compared to intervention(s)/exposure(s), placebo and/or sham therapy, non-Ayurveda interventions or combination of Ayurveda and non-Ayurveda interventions will be considered as comparators/controls.
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Outcome Measures
Primary Outcome
- Response to Ayurvedic treatment (improvement or remission in subjective and/or objective criteria of assessment).
- Serious adverse events (resulting in death, disability or incapacity, complications, were life-threatening, led to hospitalization, or prolonged hospitalization).

Secondary Outcome
- Withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment.
- Number of patients with specific adverse event.

Types of Study to be Included
Randomized controlled trials (RCTs), multiple arms clinical trials, quasi-experimental trials (nonrandomized controlled clinical trials and before after studies), and observational studies (case series and case reports, especially to know any adverse event of therapy).

Exclusion Criteria
- Preclinical studies, qualitative studies, and literary studies conducted in this area.
- Published documents written in any regional languages will be excluded.
- Animal trials, editorials and opinions, abstracts only, where insufficient methodological details are reported.

Search Methods for Identification of Studies
A predefined search strategy will be used for the identification of the studies in the following manner:

Electronic Search
PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), Digital helpline for Ayurveda research articles (DHARA), Google Scholar, and online clinical trials registers will be searched in English, Hindi, and Sanskrit language. Studies published (from the date of inception till the date the searches are run will be sought) between January 1990 and the date the searches are run will be sought. The searches will be rerun just before the final analyzes and further studies retrieved for inclusion.

Searching Other Resources

Search Strategy
Search strategy combining MeSH terms and free-text words using the Boolean operators "AND" and "OR" will be used, such as "AYURVED* OR AYURVED "depression", "major depressive disorder", "moderate depression", "mild depression", "mild to moderate depression" OR "kahomnada" "vishada" AND "Ayurvedic", "complementary medicine", "natural", "herbal medicine", "phytomedicine", "phytotherapy", "herbs", "diet", "food", AND "randomis(z)ed. control trial", "quasi trial", "clinical trial", "before after trial", "pre post test trial", "case control", "case series", "RCT" as title, abstract, or keyword.

Furthermore, the references in the studies will be examined for additional relevant articles.

Data Collection and Analysis
Selection of Studies
Three reviewers will independently review the titles and abstracts of all references. The reference section of the included studies will be scanned to sort in additional studies. These three reviewers will independently screen the full texts of all these articles to determine inclusion/exclusion. The studies that are not meeting the established inclusion/exclusion criteria will be excluded. Potentially eligible articles will be read in full to reevaluate and disagreements will be discussed with the fourth reviewer. If necessary, additional information will be obtained from the contact person (authors) of that study through e-mail or telephone. The reasons for exclusion of the trials will be recorded. A PRISMA flow diagram will be prepared to show the overall process of study selection and the number of citations reviewed at each stage of this review (Flowchart 1).

Data Extraction
The data mined by three reviewers separately, cross-checked, and with dissolved disagreements will be extracted or organized in a predesigned Excel sheet with the following details:
- General information: Data related to name of the disease/area, title of the study, name of the author (coauthor/corresponding author), place of study, year of study, and publication.
- Methodology in brief: Study design, study period, sample size.
- Characteristics of the population: Number of participants randomized, age, sex, disease duration.
- Intervention characteristics: Dose, root of administration, time of administration, duration.
- Control characteristics: Ayurveda treatment (Shamana or/ and Shodhana) with different dose, type, schedule, medicine/placebo and/non-Ayurveda interventions or combination of Ayurveda and non-Ayurveda interventions.
- Approval of ethics committee, registration status (Clinical Trial Registry of India).
- Data on outcome variables: All outcomes assessed by the reviewers in terms of improvement or remission in subjective and/or objective criteria of assessment, serious adverse events, withdrawals, number of patients with specific adverse event, drop outs.

Risk of Bias (Quality) Assessment
Three review reviewers will independently assess the risk of bias in included studies. Randomized controlled trials will be assessed with the help of Cochrane tool of Risk of bias and that of nonrandomized trials will be assessed with ROBINS-I tool (Risk Of Bias In Non-randomized Studies—of Interventions). Disagreements between these reviewers will be resolved by discussion, with involvement of a fourth reviewer if necessary and the results will be interpreted.

All four reviewers will assess the quality of reporting trial independently as follows:
Flowchart 1: PRISM flow diagram

- CONSORT (Consolidated Standards of Reporting Trials)-2010 checklist for quality assessment of included parallel group randomized clinical trial.
- TREND (Transparent Reporting of Evaluations with Non-Randomized Designs)-2004 checklist for quality assessment of included nonrandomized trial.

Assessment will be performed under three categories, “Yes” reporting, “No” reporting, and “Incomplete” reporting. Two points will be given for each item if it is reported completely, in case of incomplete reporting only one point will be given to that item, and no point for “No” reporting. Results will be interpreted in terms of percentage (%) of mean of each three category reporting items. If any disagreement still persists causing difficulty in data extraction clarification will be sought from the authors of the trial.

Strategy for Data Synthesis
Three investigators including consultants (statisticians) will analyze the data using appropriate software. Dichotomous data will be presented and combined using relative risks, continuous data will be summarized by arithmetic means, and standard deviations data will be combined using weighted mean differences, and both will be accompanied by 95% confidence intervals.

Medians and ranges will be reported in tables. Arithmetic means and standard deviations will be used to summarize continuous data, when the data are assumed to be normally distributed. Separate summary effect estimates will also be generated for studies that meet and do not meet the individual quality criterion.

Heterogeneity among trials will be assessed by inspecting forest plots, to look for overlapping confidence intervals, applying the $\chi^2$ test, with a p value of 0.05, indicating statistical significance, and using the $I^2$ test with a value of 50%, used to denote moderate levels of heterogeneity. If heterogeneity is detected, and if sufficient studies are included and included in this review, and it is still considered to be clinically meaningful to combine studies, then a random-effects model will be used in a meta-analysis based on the methodological quality of the studies. For individual trials, wherever possible, mean differences (and 95% confidence intervals) will be reported.

The reviewers will narratively synthesize the results and present the results in count, percentage, and frequency. A sensitivity analysis, to investigate the robustness of the results to the quality components, will also be carried out, provided there are sufficient trials. A funnel plot will be utilized to indicate publication bias, heterogeneity of results, or differences in methodological quality.

Analysis of Subgroups or Subsets
If the data are available, a predefined subgroup analysis will be conducted to assess the heterogeneity of different studies, including the following:
- Type of depression (mild/moderate/severe).
- Duration or chronicity of depression.
- Type of Ayurveda intervention.
- Type of control.
- Age group.

Managing Missing Data
In cases where data about details of on study design, population, intervention, or outcomes are missing, the authors of the included studies will be contacted by e-mail or telephone to request additional information or clarification. Missing data from the original authors will be requested, whenever possible. If it is not possible to do this, only the available data will be analyzed as it is and reported as limitations of study.

Discussion
The proposed protocol for systematic review of efficacy and safety of Ayurveda interventions in the management of depression is aimed to apply a transparent and reproducible procedure. In research, the evidence generated through systematic review and meta-analysis is regarded as of the highest level; however, in the field of Ayurveda, this sought of evidence is meager and in depression it is unavailable. The study protocol clearly describes the need for conducting the systematic review, the research question to be answered, objectives of the study, and the methods adopted to conduct it, such as the types of studies to be included, participants, interventions, and outcomes that will be included, data
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RESULTS
The review is going on and after its completion; it will be published in a peer-reviewed journal. It will also be disseminated electronically and in print.

STUDY REGISTRATION
In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on March 30, 2020 and registration number is CRD 42020139382.

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AUTHOR’S CONTRIBUTION
All the authors have significantly contributed in the development of protocol.

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हिन्दी सारांश

अवसाद के लिए आयुर्विद चिकित्सा की प्रभावोत्पादकता और सुरक्षा: एक सिस्टेमेटिक रियू प्रोटोकॉल

सुधा के चिनूवरी, अश्विन सी चिनूवरी, किशोर पी पटेल, साक्षी शर्मा

प्रस्तावना: अवसाद एक सार्वजनिक स्वास्थ्य महत्व का प्रमुख विकार है। आयुर्विदिक विज्ञान के व्यापक रूप से निर्धारित अवसादीय औषधियां अवसाद को प्रभावित रूप से प्रभावित करने में अपरिचित हो रहे हैं। आयुर्विदिक शोध अध्ययनों से पता चलता है कि अवसादस्तर रोगी अन्य उपचार विकल्पों जैसे कि पूर्व- और वैकल्पिक चिकित्सा (एयरएम शर्मा) का उपयोग करने पर संदर्भ करते हैं। यद्यपि इस विषय पर व्यवस्थित समीक्षा सीएम शर्मा के लिए प्रकाशित की गई है, परन्तु आज तक आयुर्विद चिकित्सा अध्ययनों पर कोई विशेष अध्ययन उपलब्ध नहीं हैं। इसलिए, वर्तमान अध्ययन का उद्देश्य यह है कि अवसाद के प्रबंधन में आयुर्विदिक चिकित्सा की सुरक्षा, प्रभावशाली या प्रभावोत्पादन वे कितने प्रकाशित नैदानिक डेटा का सिस्टेमेटिक रियू करना है और उपयुक्तता अनुसार योग्य अध्ययनों का मेटा-एनालिसिस भी किया जाए।

सामग्री और विधियां: रेडमाइज़ क्रिंतिकल ट्रायल (आरसीटी), मल्टीपैल्यू आर्म्स क्रिंतिकल ट्रायल, ट्रायल क्वालिटी-एस्केपरिमेंटल ट्रायल और विश्लेषणात्मक अध्ययन (केस-सीरीज और केस-कंट्रोल) के व्यवस्थित समीक्षा PubMed, कोक्रेन लाइब्रेरी, आयुर्विदिक रिसर्च पोर्टल, धारा, गूगल स्कॉर्नर और ऑनलाइन क्रिंतिकल रजिस्ट्री जैसे डेटाबेस के माध्यम से की जाएगी। डेटा बेल्स के प्रारंभ से लेकर, जब तक खोज की जाएगी तब तक के उपलब्ध शोध अध्ययनों को शामिल किया जाएगा। अध्ययन का चयन, डेटा पुष्करण, और संयंत्र लेखकों द्वारा स्वतंत्र रूप से किया जाएगा और किसी भी असहमति पर टीम द्वारा चीफ समीक्षा लेखक के साथ आम सहमति तक पहुंचने के लिए चर्चा होगी। अध्ययन के चयन, गूणवत्ता मूल्यांकन और नेरेटिव सिंपोजियस के लिए स्थापित दिशानिर्देश का पालन किया जाएगा। पूर्ववर्त में जोखिम का मूल्यांकन कोक्रेन रिसर्च ऑफ बायस ट्रायल के सहायता से किया जाएगा। अध्ययन के परिणामों को वर्तमान स्तर पर संशोधित किया जाएगा और संस्थान, अनुसंधान और आयुर्विदिक अनुसंधान प्रबंधक अध्ययन के लिए मेटा-एनालिसिस के योजना बनाई जाएगी। भीमों को अध्ययन के किसी भी चरण में शामिल नहीं किया जाएगा। हालांकि, संस्थान नैतिक समीक्षा से अनुमोदन प्राप्त किया गया है।

प्रस्ताव: प्रस्तुत समीक्षा को पिंठ रियू जर्मन में इलेक्ट्रॉनिक तथा प्रिंट माध्यम में प्रकाशित किया जाएगा। यह समीक्षा अवसाद की आयुर्विदिक चिकित्सा द्वारा स्वास्थ्य देखभाल प्रथाओं और नैतिक नियमों में सहयोग सिद्ध हो सकती है।

अध्ययन पंजीकरण संख्या: PROSPERO-CRD4202013938

कुंजी शब्द: आयुर्विद, अवसाद, कोक्रेन, सिस्टेमेटिक रियू, सिस्टेमेटिक रियू प्रोटोकॉल, विषय।