

A Protocol for a Systematic Review to Study the Efficacy and Safety of Ayurveda Intervention in Children and Adolescent with Attention-deficit/Hyperactivity Disorder



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ABSTRACT

Background: Various clinical researches have been done in Ayurveda to study the effectiveness of Ayurveda intervention in attention-deficit/hyperactivity disorder (ADHD), one of the most common neurodevelopmental disorders in pediatric population. However, to date, no comprehensive systematic review has been conducted to assess the quality of clinical trials conducted and to determine the strength and safety of Ayurveda interventions in ADHD.

Materials and methods: Published randomized clinical trials (RCTs), non-RCTs, and unpublished data on Ayurveda intervention in ADHD will be searched by using electronic databases such as the Cochrane Library, Pubmed, CENTRAL, Science Direct, AYUSH research portal, and other Indian databases. It involves the hand-searching of Ayurveda journals, and PG/PhD dissertations, if available, will also be utilized. The selection of study, data extraction, and synthesis will be done independently by reviewers. Standard tools will be adopted to assess the quality of trials. Risk of bias assessment will be performed by using Cochrane tool of risk of bias for RCTs and risk of bias in non-randomized studies of interventions (ROBINS-I) tool for non-RCTs. A narrative synthesis of findings from included studies will be described by providing treatment effect size. If sufficient data are available, the meta-analysis will be performed by using Review Manager.

Outcome: The proposed protocol will act as a guiding tool for reproducing the same results in a transparent manner and to provide information to healthcare practitioners and policy makers.

Trial registration number: PROSPERO 2019 CRD42019129676.

Keywords: Attention-deficit/hyperactivity disorder, Ayurveda, Ayurvedic intervention, Meta-analysis, Systematic review.

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INTRODUCTION

The attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children and adolescent, with increasing incidence rates.¹ According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) of the American Psychiatric Association (APA), ADHD is characterized by persistent pattern of inattention and/or hyperactivity-impulsivity that is frequently displayed and more severe than typically observed in individuals at a comparable level of development.^{1,2} Worldwide, estimated prevalence ranges between 6% and 8% among school-aged children, with boys being more likely than girls to develop ADHD.³ In India, its prevalence is likely similar to other countries.³ The symptoms of ADHD usually become evident in preschool or early years; however, the median age of onset is 7 years.⁴ For many individuals, ADHD symptoms improve during adolescence as age increases, but the disorder can persist into adulthood.

Attention-deficit/hyperactivity disorder has negative impact on children and their parent's lives and also inflicts financial cost to the community. It also causes social problems for children such as weak peer relationship, low self-esteem, poor academic performance, and low quality of life.⁵

Several approaches are available to manage ADHD, but the pharmacotherapy is the standard approach by using psychostimulant drugs such as amphetamine/methylphenidate and tricyclic antidepressants (TCAs) such as imipramine and nortriptyline.⁶

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The major side effects of methylphenidate are loose motion, anorexia, insomnia, etc., whereas TCAs can cause anticholinergic side effects such as dry mouth, constipation, mental confusion, weight gain, convulsion, etc. Unfortunately, children with ADHD are highly at risk of substance abuse disorders.^{6,7} The outcomes with these approved medications for ADHD are often unsatisfactory and have left empty space for others to be filled by alternative medicine especially traditional system of medicine or herbal medicine.

Accordingly, there is growing considerable interest among parents in children with ADHD to seek complementary and alternative medicine.⁸ Ayurveda, a well-known Indian system of

traditional medicine practiced since ages, is favorably accepted by parents in Indian population as an alternative or complement to conventional treatment approach because of better cultural acceptability and with perception of no side effects or less harmful than modern pharmaceutical agents. There are no direct references of this disorder in Ayurvedic texts. However, some references can be traced to terms described about abnormal behavior under the feature of *Vata Prakriti*, definition of *Unmada* (insanity) such as *Anavasthitha chittatva*, *Manovibhrama*, *Buddhivibhrama*, *Smritivibhrama*, *Sheelavibhrama*, *Chestavibhrama*, and *Acharavibhrama*. Its etiology in modern medicine is still obscure, while from Ayurveda perspective, considering the nature of symptomatology manifestation, it may be due to vitiation of *Dhee* (rational thinking), *Dhriti* (intellect/retaining power of the mind), and *Smriti* (memory) which causes abnormal conduct resulting in improper contact of the senses with their objectives and giving rise to inattention, hyperactivity, and impulsivity. Ayurveda intervention for ADHD typically comprises multimodal approach by using a combination of different types of medicine as internal or external application and or Panchakarma procedures, depending upon the dominance of *Doshas* (biological humors of body, namely, *Vata*, *Pitta*, and *Kapha*).

In recent years, various publications in Ayurveda field have explored this area and found significant results in terms of effectiveness. However, to date, no comprehensive systematic review has been conducted to assess the quality of studies published and the strength of clinical efficacy and safety of Ayurvedic medicines. Understanding the efficacy and safety of Ayurveda intervention will allow appropriate recommendation of Ayurvedic treatment of children with ADHD.

Objectives

We propose to undertake systematic review of the published clinical data in view of safety and efficacy of Ayurvedic intervention for the treatment of ADHD in children and adolescents. If a large number of studies are available, meta-analysis will be performed.

MATERIALS AND METHODS

Criteria for Considering Studies for this Review

Type of Studies

Randomized controlled trials, quasi-RCTs, controlled clinical trials, and comparative clinical trials will be included. Cluster randomized clinical trials (RCTs), case series, case reports, uncontrolled clinical trials, and other qualitative studies will be excluded. Trials that do not provide detailed results or repeated attempt has been made to review authors for providing incomplete data/to seek more information on results will also be excluded. Postgraduate dissertations and other unpublished clinical data will also be included if it contains sufficient data for critical evaluation. Data available as full and in English/Indian language will be considered eligible.

Type of Participants

The studies that evaluated children and adolescent of age 5 to 18 years, diagnosed with ADHD irrespective of its subtypes (combined type, predominantly inattentive and predominantly hyperactive/impulsive) will be included. The diagnosis of ADHD should be based on the criteria of Diagnostic and Statistical Manual of Mental Disorders or the International Statistical Classification of Diseases.

Patients having ADHD with comorbid conditions (such as anxiety, depression, epilepsy) and other associated medical conditions will be considered eligible for inclusion.

Type of Intervention

We will include those trials using Ayurvedic intervention alone or in combination with conventional treatment; or placebo/sham treatment; or combination of Ayurveda and non-Ayurveda intervention; or Ayurveda intervention as comparator in comparative clinical trials. The term Ayurveda intervention includes treatment/practices based on fundamental principles of Ayurveda by means of usage of internal or external medications, Panchakarma therapy, lifestyle advocacy, diet therapy, and others; intake of herbs/medicinal plants described in Ayurvedic literature or found in Indian subcontinent; as single herb, polyherbal, or herbomineral or metallic formulation or in any extract form (such as powdered, decoction, tablet, butter oil, etc.) of any dosage, vehicle, and duration of treatment. Treatments other than Ayurveda, such as homeopathy, Yoga, Chinese traditional medicine, Siddha system of medicine, Unani system of medicine, and other systems of medicines practiced worldwide not based on fundamental principles of Ayurveda will be excluded.

Type of Outcome Measures

The following outcome measures will be assessed based on the analyses of data obtained in the included trials.

Primary Outcome:

- Efficacy—improvement noted in ADHD symptoms from baseline to last follow-up by using Conner's rating scale, ADHD rating scale, or any other validated or published scale used as a primary or secondary outcome.
- Safety—patient/parent or laboratory-based reporting of adverse events.

Timing and effect measures—no restrictions will be made in inclusion of study in review on the basis of outcomes mentioned above.

Secondary Outcome:

- Number of participants withdrawing from the trial due to adverse event or ineffectiveness of treatment.
- Number of participants dropping out of from the trial.
- Number of participants experiencing any adverse event.
- Number of participants with specific adverse events.

Timing and effect measures—no restrictions in inclusion of study for review on the basis of outcomes mentioned above.

Search Method for Identifying the Studies

Attempt will be made to find all relevant trials published online and off-line between January 2000 and to date. The search will be rerun just before the final analyzes and further studies are retrieved for inclusion. The search will be restricted to publication in English/Indian language.

The following electronic database will be searched online by using PubMed, The Cochrane Library, the Cochrane central register of controlled trials (CENTRAL), Google Scholar, and ScienceDirect. We will also search Indian databases such as AYUSH Research Portal, Digital Helpline for Ayurveda Research Articles, ShodhGanga: a reservoir for Indian theses, and research in Ayurveda—online

directory of PG and PhD titles. In addition to identifying ongoing studies, we will search ClinicalTrials.gov, the Clinical Trials Registry of India, and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal for ongoing or completed trials.

We will also hand search selected journals of Ayurveda including the Journal of Research in Ayurveda and Siddha, Journal of Ayurveda, Ancient Science of Life, Journal of Drug Research in Ayurvedic Sciences, and AYU (an International Quarterly Journal of Research in Ayurveda) to complement the electronic search.

Further the bibliographic references of all the included trials will be reviewed to identify other relevant studies. An attempt will also be made to contact the authors of the trial studies and experts in the field.

Search Strategy

The search strategy will include only key terms relating to or describing the intervention "Ayurved*" in combination with search term describing the diseased condition "ADHD." The search term for each database will be adapted for use with database-specific filters. The following search algorithm will be adopted ["Ayurvedic medicine" OR "Medicine, Ayurveda" OR "Ayurveda" OR "Ayurvedic" OR "Hindu Medicine" OR "Ayurveda intervention" OR "Ayurveda therapy" OR "Ayurveda Herbs" OR "Ayurvedic drugs" OR "AyurvedicFormulation" OR "Ayurveda Plants"] AND ["ADHD" OR "adhd" OR "Attention-deficit/hyperactivity disorder" OR "Attention-deficit disorder" OR "Attention-deficit/hyperactivity disorder" OR "Hyperkinetic syndrome" OR "Attention-deficit disorder with hyperactivity"] as title/abstract/keyword.

Data Collection and Analysis

Selection of Studies

Three of the review authors (KC, PD, and SG) will independently assess titles and/or abstracts of studies retrieved using the search strategy and those from additional sources. After exclusion of duplicates from eligible articles, full-text articles will be retrieved and reviewed completely to determine whether they meet the inclusion and exclusion criteria as outlined. Any disagreement between the eligibility of particular studies will be resolved through discussion with a fourth reviewer (MG). If essential information is found missing/or unclear or to be sought from particular study, an attempt will be made to contact trial author via e-mail or telephone for getting details. If records could not be obtained from trial author, the study will be excluded. Excluded studies will be documented with reasons for their exclusion. The details of selection process will be shown in Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

Data Extraction and Management

A data extraction form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include details such as study setting; study population, and participant demographics; details of intervention and control/comparator; study methodology; outcomes; suggested mechanism of intervention action, etc. in accordance with the standard guidelines—PRISMA and the recommendation of the Cochrane collaboration. Three review authors (KC, PD, and SG) will independently extract data, and any discrepancy identified will be resolved through discussion or in consultation with the fourth reviewer (MG) wherever necessary.

When the reported data are insufficient or ambiguous, the corresponding author of the clinical trial will be contacted by e-mail or telephone to request for additional information or clarification.

Assessment of Quality of Study Trials Included

Three of the review authors (KC, PD, and SG) will independently assess the quality of study trial included by adopting standard tools such as consolidated standards of reporting trials—2010 checklist for RCTs and transparent reporting of evaluations with non-randomized designs—2004 checklist for nonrandomized trial and any other if required. If necessary, we will contact the trial authors for any clarification. Any differences in opinion will be resolved by discussion with the fourth review author (MG).

Assessment of Risk of Bias in the Included Studies

Three of the review authors (KC, PD, and SG) will independently assess the risk of bias in the eligible studies as proposed by Cochrane collaboration. The RCTs will be assessed with the help of Cochrane tool of risk of bias which are classified as low, unclear, or high risk of bias by evaluating criteria such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Those of nonrandomized trials will be assessed by risk of bias in non-randomized studies of interventions (ROBINS-I) tool, which is guided through seven chronologically arranged bias domains (preintervention, at intervention, and postintervention) and the interpretation of domain level and overall risk of bias judgment classified as low, moderate, serious, or critical risk of bias. If necessary, we will contact the authors of eligible trial for clarification. Any differences in opinion will be resolved by discussion or arbitration involving a fourth review author (MG). The findings in risk of bias will be summarized as summary graph or figure.

Descriptive Analysis

A narrative synthesis of the findings from the included studies structured around the type of intervention, target population characteristics, type of outcome, and intervention content will be presented in the final review. All treatment effect sizes will be transformed into common metrics to make them comparable across all the studies. For continuous data, we will use mean difference (MD) to measure the treatment effect at a 95% confidence interval (CI). In cases of outcomes with different scales, we will use the standard MD with a 95% CI. For dichotomous data, we will present the treatment effects as relative risk or risk difference with 95% CIs.

Statistical Analysis

The study aims to find the effectiveness and safety of Ayurveda intervention in children and adolescent diagnosed with ADHD. Considering the diversity of Ayurvedic intervention and the range of different outcome measures across the small number of existing studies, we anticipate that there will be little scope for meta-analysis. However, if large numbers of publication are found and data permit, the meta-analysis will be carried out. If meta-analysis is possible, we will use I^2 statistic to quantify the inconsistencies among the included studies. An I^2 value of more than 50% will be considered indicative of substantial heterogeneity. If heterogeneity is observed, we will conduct a subgroup analysis to explore its possible causes. Data synthesis

for studies which are sufficiently homogeneous with respect to their population, intervention, comparison and outcome (PICO) and study designs will be performed by using Review Manager (RevMan), V.5.2.6. The overall treatment effect will be estimated by using random effect model in case of moderate to severe heterogeneity, otherwise fixed effect model will be used. We will use forest plot for graphical display of result from individual studies and estimate of the overall treatment effect. In addition, the presence of publication bias will be assessed by using Funnel plot, if sufficient studies are available.

DISCUSSION

Till date, no systematic review has been conducted to study the effectiveness and safety of Ayurveda intervention in children and adolescent with ADHD. The proposed systematic review will provide evidence for the effectiveness and safety of Ayurveda intervention and help to generate database to explore further areas of research in terms of outcome results observed with different types of Ayurveda treatment modalities as stand-alone or in combination with conventional treatment practiced in ADHD.

The proposed protocol will act as a guide tool for reproducing same results in a transparent manner for the systematic review of ADHD in children. We have clearly described the procedures incorporated for inclusion and exclusion of type of studies, search strategy, data extraction, and data analysis. By publishing protocol, we reinforce the clarity of the strategy and to minimize the bias, especially selective outcome reporting. This review paper will provide outlook for the pros and cons of the trial study planned, the study design methodology adopted, the outcome parameters measured and also serve as a tool for the future clinical trials for planning effective study design in order to generate higher level of evidence.

The publication of systematic review in peer-reviewed journal will be disseminated electronically and in print to reach physicians and general public in order to provide information and guide for decision-making policy makers.

LIMITATION OF STUDY

Due to the availability of less number of RCTs of Ayurveda intervention in children with ADHD, the meta-analysis may negatively influence the statistical power in data synthesis.

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REFERENCES

1. Polanczyk GV, Willcutt EG, Salum GA, et al. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol* 2014;43(2):434–442. DOI: 10.1093/ije/dyt261.
2. Vahia VN. Diagnostic and statistical manual of mental disorders 5: a quick glance. *Indian J Psychiatry* 2013;55(3):220–223. DOI: 10.4103/0019-5545.117131.
3. Gentile JP, Atiq R, Gillig PM. Adult ADHD: diagnosis, differential diagnosis, and medication management. *Psychiatry (Edgmont)* 2006;3(8):25–30.
4. Bhalerao S, Munshi R, Nesari T, et al. Evaluation of Brāhmī ghrtam in children suffering from attention deficit hyperactivity disorder. *Anc Sci Life* 2013;33(2):123–130. DOI: 10.4103/0257-7941.139057.
5. Harpin VA. The effect of ADHD on the life of an individual, their family, and community from preschool to adult life. *Arch Dis Child* 2005;9(Suppl 1):i2–i7. DOI: 10.1136/adc.2004.059006.
6. Spencer T, Biederman J, Wilens T, et al. Pharmacotherapy of attention deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry* 1996;35(4):409–432. DOI: 10.1097/00004583-199604000-00008.
7. Hardman J, Limbard L, ed. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 10th ed., New York: McGraw Hill Medical Publication Division; 2001. p. 236.
8. Barnes PM, Bloom B, Nahin RL. Complementary and alternative medicine use among adults and children: United States, 2007. *Natl Health Stat Report* 2008;10(12):1–23.

हिन्दी सारांश

बाल एवं किशोरावस्था में अटेंशन डेफिसिट हाइपरएक्टिविटी डिसऑर्डर के लिए आयुर्वेद चिकित्सा पद्धति की सुरक्षितता एवं प्रभावकारिता सिस्टेमाटिक रिव्यू के लिए प्रोटोकॉल

कुलदीप चौधरी, पार्थ पी. दवे, सुमीत गोयल, मनोहर एस. गुंडेटी

परिचय: विविध चिकित्सा अनुसन्धान द्वारा आयुर्वेदीय चिकित्सा पद्धति का बालकों में पाए जाने वाले सबसे आम न्यूरोडेवेलपमेंटल विकारों में से एक अटेंशन डेफिसिट हाइपरएक्टिविटी डिसऑर्डर (एडीएचडी) पर प्रभावशाली अध्ययन पाया गया है। हालाँकि, आज तक इन शोध पत्रों में उल्लेखित अनुसन्धान विधि की गुणवत्ता का आकलन एवं आयुर्वेदीय चिकित्सा पद्धति की प्रभावकारिता एवं सुरक्षितता का निर्धारण करने के लिए कोई व्यापक समीक्षा नहीं की गयी है।

विधि और विश्लेषण: हम एडीएचडी के लिए आयुर्वेद चिकित्सा पद्धति के प्रकाशित आरसीटी, नॉन-आरसीटी एवं अप्रकाशित साहित्य की चिकित्सा व अनुसंधान कार्य की व्यवस्थित समीक्षा (सिस्टेमाटिक रिव्यू) करेंगे। इस कार्य में निम्नलिखित इलेक्ट्रॉनिक डेटाबेस जैसे कोक्रेन लाइब्रेरी, पबमेड, सेंट्रल, साइंस डायरेक्ट, आयुष रिसर्च पोर्टल एवं अन्य भारतीय डेटाबेस की सहायता ली जाएगी, साथ में आयुर्वेद पत्रिका और पीजी./पीएचडी शोध प्रबंधों को भी खोजा जाएगा। ट्रायल्स की गुणवत्ता का आकलन करने के लिए मानक उपकरण अपनाए जाएंगे। रिस्क ऑफ बायस परीक्षणार्थ, आरसीटी के लिए कोक्रेन टूल ऑफ रिस्क ऑफ बायस एवं नॉन-आरसीटी के लिए रॉबिन्स -1 टूल की योजना होगी।

परिणाम: शामिल अध्ययनों से निष्कर्षों का एक कथा संश्लेषण एवं उपचार के प्रभाव का वर्णन किया जायेगा। यदि पर्याप्त और उचित डेटा उपलब्ध है, तो रिव्यू मैनेजर सॉफ्टवेयर का उपयोग कर मेटा एनालिसिस किया जाएगा।

निष्कर्ष: प्रस्तावित प्रोटोकॉल पारदर्शी तरीके से समान परिणामों को पुनःपेश करने और स्वास्थ्य चिकित्सकों और नीति निर्माताओं को जानकारी प्रदान करने के लिए मार्गदर्शक उपकरण के रूप में कार्य करेगा।