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Title:

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Date:

2022-02-01

Citation:

Kean, J. D., Downey, L. A., Sarris, J., Kaufman, J., Zangara, A. & Stough, C. (2022). Effects of Bacopa monnieri (CDRI 08®) in a population of males exhibiting inattention and hyperactivity aged 6 to 14 years: A randomized, double-blind, placebo-controlled trial. *Phytotherapy Research*, 36 (2), pp.996-1012. <https://doi.org/10.1002/ptr.7372>.

Persistent Link:

<https://hdl.handle.net/11343/336295>

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Effects of CDRI 08® in male children

Effects of Bacopa monnieri (CDRI 08®) in a population of males exhibiting inattention and hyperactivity aged 6 to 14 years: A randomised, double-blind, placebo-controlled trial

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/ptr.7372](https://doi.org/10.1002/ptr.7372)

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Abstract

The current study investigated the efficacy of extract of *Bacopa monnieri* (BM; CDRI 08®) in reducing levels of inattention and hyperactivity in young children. BM has demonstrated improvements in cognitive outcomes in adults, yet little research is available on its effects in younger populations. A 14-week randomised, double-blind, placebo-controlled clinical trial, with placebo run-in and run-out phases, investigated the effects of BM on behavioural, cognitive, mood, and sleep effects in male children aged 6 to 14 years against placebo. One-hundred and twelve participants were recruited into the trial, with 93 datasets available for analysis. No significant behavioural differences were noted between treatment groups. Cognitive outcomes indicated decreased error-making in children taking CDRI 08® ($p = .04$) and increased speed of reaction time in those taking placebo ($p = .04$) at study end. Improvements in cognitive flexibility ($p = .01$), executive functioning ($p = .04$), interpersonal problems ($p = .02$), and sleep routine ($p = .04$) were noted in those consuming CDRI 08® over placebo. CDRI 08® did not improve behavioural outcomes, but may have cognitive, mood and sleep benefits in children aged 6 to 14 years. Further study is required to support the findings presented here.

Keywords: ADHD, attention, behaviour, bacopa, cognition, children

Introduction

Symptoms of attention-deficit/hyperactivity disorder (ADHD) can often lead to significant personal distress and functional impairment (American Psychiatric Association, 2013; Selinus et al., 2016). Validated ADHD assessments enable clinicians the ability to verify clinical levels of ADHD symptoms including hyperactivity, impulsivity, and inattention. However, despite exhibiting moderate levels of these symptoms, children with behavioural challenges often fall short of this clinical cut-off (Selinus et al., 2016), highlighting a potential 'sub-clinical' category of children and adolescents. Recent research has indicated a prevalence for children falling within this sub-clinical category to be anywhere from 0.8% to 23% of the population (Balázs & Keresztény, 2014). This cohort of children with sub-clinical symptoms, notably have a ten-fold increase in the likelihood of experiencing severe functional impairment when compared to children exhibiting more typical behaviour and cognition for their age (Costello & Shugart, 1992). These deficits may lead to delays in cognitive development (Pfiffner et al., 2007; Volkow et al., 2011), including problems with language and understanding (American Psychiatric Association, 2013), and an increased risk of mental health problems later in life (Chen, Lawlor, Duggan, Hardy, & Eaton, 2006).

This evidence has led some researchers to consider ADHD as a cognitive disorder, rather than a behavioural one (Brown, 2005). Reframing clinical and sub-clinical ADHD in this way, stresses executive functioning as a core feature of the disorder, emphasising the need for early intervention therapies. Pharmacotherapy for ADHD includes catecholamine stimulants and non-stimulants (Sofuoglu & Sewell, 2009). Methylphenidate (MPH) is one of the most commonly prescribed stimulants for the disorder (Briars & Todd, 2016). Despite its efficacy (Snircova, Hrtanek, Kulhan, Nosalova, & Ondrejka, 2015), children exhibiting sub-clinical symptoms may be unable to access stimulants due to a lack of a diagnosis (Balázs & Keresztény, 2014).

Nutrient and complementary medicine is a rapidly growing area of innovative research. Such alternative treatments are quickly finding a home in modern medicinal journals (Ashton et al., 2021) and clinical settings. One Eastern medicinal system, Ayurveda, contains frequently researched alternatives to current Western treatments. One commonly researched medicine is *Bacopa monnieri* (L.) Wettst. (syn. *Bacopa monnieri* Hayata & Matsum), a perennial creeping herb with evidence for cognitive enhancement in adult populations (Pase et al., 2012). An extract of this herb is CDRI 08®, which has been the subject of 50 years of clinical research. Randomised, controlled trials in adult populations have demonstrated cognitive improvements in auditory verbal learning (Barbhaiya et al.,

Effects of CDRI 08[®] in male children

2008; Calabrese et al., 2008; Morgan & Stevens, 2010; Stough et al., 2001), visual perception (Calabrese et al., 2008; Stough, Downey, & Lloyd, 2008), and associative memory (Barbhaiya et al., 2008; Roodenrys et al., 2002). Findings in child and adolescent populations have reported similar findings with improvements against placebo in language behaviour (Asthana et al., 2001; U.P. Dave et al., 2008; Negi et al., 2000), visual memory (Asthana et al., 2001; U.P. Dave et al., 2008), memory span (Asthana et al., 2001; U.P. Dave et al., 2008; Sharma, Chaturvedi, & Tewari, 1987), mental speed (Asthana et al., 2001; U.P. Dave et al., 2008), and attention (Asthana et al., 2001; U. P. Dave et al., 2014) as well as behavioural improvements in hyperactivity (Asthana et al., 2001; U. P. Dave et al., 2014). Conversely, one recent meta-analysis noted a lack of consistent positive outcomes for BM in clinical samples (Brimson et al., 2021). This highlights an intriguing gap in the literature between clinical and non-clinical samples. As such, more rigorous clinical trials are required to substantiate these findings across a broader spectrum of disorder-related symptoms

Current research indicates BM promotes neuroprotection, cerebral blood flow, and modulates acetylcholine, dopamine, and serotonin neurotransmitter activity (Aguar & Borowski, 2013). BM is also reported to inhibit acetylcholinesterase and reduce beta-amyloid formation and accumulation in the brain (Limpeanchob, Jaipan, & Rattanakaruna, 2008). Based on the research into ADHD, and the purported benefits of stimulant and non-stimulant pharmacotherapy (Sofuoglu & Sewell, 2009), the reported mechanisms of action highlight the potential for BM to improve the behavioural, mood, and executive functioning of children and adolescents exhibiting symptoms of ADHD.

This study is the first to assess this specific extract of BM in a population of children and adolescents exhibiting symptoms of inattention, hyperactivity, and impulsivity. This is a chronic randomised, placebo-controlled trial of CDRI 08[®] against a placebo-equivalent measuring changes in cognition, behaviour, mood, sleep, and electrophysiology over 14-weeks in young males between 6 and 14 years of age. It was hypothesised that the treatment group would demonstrate reduced levels of ADHD symptoms, as well as improved cognitive, mood, and sleep outcomes.

Methods

Participants

A sample of 112 healthy male participants aged between 6 and 14 years were enrolled in the current study between July 2014 and December 2016, to determine the benefits of CDRI 08[®] on symptoms of attention, behaviour, cognition, mood, and sleep. Inclusion criteria were healthy, non-smoking males aged between 6 and 14 years, with a DSM-IV ADHD rating score above 15 (DuPaul, Power,

Effects of CDRI 08[®] in male children

Anastopoulos, & Reid, 1998) (completed by parent or guardian), and a Wechsler's Intelligence Scale for Children 4th Edition short form (WISC-IV-SF) above 80 (Devena & Watkins, 2012). A score of 15 points or higher on the ADHD DSM-IV rating scale established an elevated level of hyperactivity, inattention, or both. All participants could read and understand English, did not have any medical conditions (e.g., high blood pressure, diabetes, food allergies, kidney disease, liver disease and/or gastrointestinal diseases) or psychological diagnoses (ADHD, Oppositional Defiant Disorder or similar behavioural disorder were accepted), and were accompanied by a parent or legal guardian. Parents or guardians and participants provided written informed consent prior to their commencement in the trial. Participants were excluded if they were taking any medication (including stimulant medication or herbal supplements). If participants were regular users of vitamins/fish oil supplements (defined as daily intake for greater than 3 months), they were asked to maintain the same habits throughout the trial. All participants received a 14-week supply of CDRI 08[®] at conclusion of their involvement to ensure all participants had the opportunity to take the active treatment. The study was ethically approved by the Swinburne University Human Research Ethics Committee (SUHREC 2011/283) after formal approval from the Royal Children's Hospital Research Ethics Committee (RCH HREC 32205). The trial is registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR: 12612000827831).

Power Analysis

Power analysis using G*Power 3.1.2 (Erdfelder, Faul, & Buchner, 1996), determined there would be an 80% chance of discovering a medium effect size ($f=0.25$) between treatment groups with a sample size of 86 participants (alpha level = 0.05) on the primary outcome, the CPRS. Previous research reported statistical significance when using Bacopa in similar sample sizes (Stough et al., 2008), with child and adolescent studies examining the efficacy of Bacopa using smaller sample sizes ($n= 40, 28, 36, 31$) (Asthana et al., 2001; U.P. Dave et al., 2008; Negi et al., 2000; Sharma et al., 1987). Given this is the first known trial of its kind, the sample size was selected on the basis of previous effect sizes from RCTs administering Bacopa.

Treatment

This was a placebo-controlled, double-blind, parallel groups (placebo vs. CDRI 08[®]), randomized trial. Participants consumed 1 × 160 mg capsule of either BM or placebo (if between 20 and 35 kg; taken with breakfast) or 2 × 160 mg capsules of either BM or placebo per day (if over 35 kg; 1 taken with breakfast, 1 taken with dinner) for 14 weeks. This daily dose is considered safe and clinically appropriate based on past intervention research and tolerability studies (Brimson et al., 2021). There was a one-week placebo run-in and one-week placebo run-out extending the study to a total of 16

Effects of CDRI 08[®] in male children

weeks. CDRI 08[®] and placebo (made up of inert plant-based materials) were identical treatments in shape, smell, taste, and weight. The CDRI 08[®] extract was supplied by SFI Health[™] and is standardized to contain 55% bacosides (based on UV spectrophotometry). The BM plant is harvested twice a year by hand and is analysed before shipment through taxonomic evaluation, a chemical analysis of the active plant ingredient through spectrophotometry, and high-performance liquid chromatography (HPLC) analysis. None of the researchers were involved in the development, marketing, or production of the CDRI 08[®] extract.

Randomization & Blinding

All treatments were identical in appearance. Treatments were individually packaged into bottles with the participant identification number clearly labelled. Trial products were stored in a temperature controlled and monitored facility in accordance with the manufacturer's instructions. To minimize bias, this study employed both randomization and blinding. Placebo run-in (V1) and placebo run-out (V4) phases were single-blind, with researchers aware of this component. Randomization of participants to treatment groups following placebo run-in was determined by random allocation. All participants were assigned to a treatment group using a computer-generated random number generator. Eligible, recruited participants were assigned a participant number. The participant's number corresponded to the allocated treatment for that individual. Blinding was achieved by enlisting a person outside of the project to code the treatments and maintain the key to this code until data collection was completed. An emergency code break envelope was provided to the principal investigator, which was only to be opened in case of emergency. Participants' parents completed health and medical questionnaires at each visit to monitor for adverse events.

Placebo run-in and run-out

Each participant consumed placebo for one week, which was then followed by their pre-randomised treatment allocation for 14-weeks, and concluded with one week's placebo treatment. The bookended placebo run-in and run-out were done so to reduce the level of placebo-responders often seen in similar trials (Sarris et al., 2013).

Measures

Conners' Parent Rating Scale

The primary outcome measure was the *Conners' Parent Rating Scale* (CPRS), to be completed by the parent or guardian on five occasions (see Table 1). The CPRS is a 110-item questionnaire that determines a child's level of inattention and impulsivity/hyperactivity, and highlights any issues with learning, executive functioning, peer relations or aggression (C.K. Conners, Sitarenios, Parker, &

Epstein, 1998). The CPRS is a valid and reliable measure with high test-retest reliability and effective discriminatory power that determines a child's symptom severity through raw score conversion to t-scores based on their age and gender across a range of symptoms including inattention, hyperactivity, executive function, learning problems, aggression, conduct disorder, oppositional defiant disorder, peer relations, impairments in relationships, school, and home life, a global ADHD, and an ADHD probability score (C. Keith Conners, Pitkanen, & Rzepa, 2011).

--- Table 1 about here---

DSM-IV ADHD Rating Scale

The ADHD rating scale is a parent-rated inventory of the child's behaviour based on the DSM-IV criteria for ADHD (DuPaul et al., 1998). The assessment factors in the child's behaviour over the previous 6-months and provides outcomes for inattention and hyperactivity/impulsivity. A score of 15 points or higher on the scale allowed investigators to establish that participants had elevated levels of hyperactivity, inattention, or both. Odd numbered questions represent the inattention subscale, while even numbers represent the hyperactivity-impulsivity subscale. The results are described in terms of subscales, total score, and percentile ranks for each score (DuPaul et al., 1998).

CNS Vital Signs

The CNS Vital Signs (CNS-VS) is a computerized test battery that enables researchers to gain insight into cognitive dysfunction and possible neurological disorders that is sensitive to medication effects (Gualtieri & Johnson, 2006). The CNS-VS assesses visual and verbal memory, reaction time, motor speed, processing speed, simple attention, and executive function. Subtests include verbal memory test (VBM), visual memory test (VIM), finger tapping test (FTT), symbol digit coding (SDC), the Stroop test (ST), shifting attention test (SAT), and a continuous performance test (CPT). The program also calculates functional outcomes across domains that encompass multiple sub-tests, see table 2 for descriptions. The assessment concludes with a symptom checklist completed by the parent or guardian regarding the presence of ADHD related symptoms exhibited by the participant at the time of their visit. The entire assessment is conducted on a desktop computer using the keyboard for responses.

--- Table 2 about here---

The Hick's Reaction Paradigm (Jensen Box)

Effects of CDRI 08[®] in male children

The *Hick Reaction Paradigm* assesses decision time (DT), movement time (MT), mental speed and rate of information processing using simple and choice reaction times. The box was created by at Swinburne University specifically for this trial. These two outcomes, DT and MT, also known as Hick's Law and Fitt's Law, describe the time taken to make a decision based on the number of choices a person has (DT) (Fitts, 1992), and the time it takes to move to their desired target based on the distance they have to travel (MT) (Hick, 1952; Hyman, 1953). The standard box has a sloping face on which 8 buttons are arrayed in a semi-circle, with a 'home' key in the lower centre. Participants are required to keep the 'home' button pressed down until a target light appears. When this target light appears, the participant releases the home button and presses the target button with the same finger as fast as possible. The Jensen Box is an assessment of mental speed and declines in difficulty as the measure progresses (from 8-choice reaction time, to 4-choice, to 2-choice, to a single choice) and provides a measure of rate of information processing (Jensen, 1987). At each stage there are 16 responses. Previous research has highlighted its efficacy in detecting changes following intervention (Camfield et al., 2013).

Paediatric Sleep Problem Survey Instrument

The Paediatric Sleep Problem Survey Instrument (PSPSI) provides a robust set of sleep problem subscales, which is used in the assessment of sleep concerns in a community sample as well as provide for optimal analysis of associations with other measures of childhood daytime functioning such as neurocognition and behaviour (Biggs, Kennedy, Martin, Van den Heuvel, & Lushington, 2012). The questionnaire reports on six subscales including sleep routine, bedtime anxiety, morning tiredness, night arousals, sleep-disordered breathing, and restless sleep. Questions were rated on a four-point Likert scale of *Never*, *Rarely* (once per week), *Sometimes* (2–4 times per week), or *Usually* (5–7 times per week). Domain scores were garnered through summing all items within each subscale (Biggs et al., 2012).

Children's Depression Inventory

The Children's Depression Inventory (CDI) is a 28-item assessment that investigates emotional and functional problems including subscales of negative mood and physical symptoms, negative self-esteem, interpersonal problems, and ineffectiveness (Kovacs, 1985). These questionnaires were completed by the participant with assistance from the parent or guardian when needed. Normative data was based on U.S. school children between the ages of 7 to 17 (Kovacs, 1985), with follow-up studies exploring its use in children aged 6 to 17 years (Nelson, Politano, Finch, Wendel, & Mayhall,

Effects of CDRI 08[®] in male children

1987). Scores are tabulated by the researcher or clinician, who uses conversion tables based on normative data to convert the total raw scores to t-scores.

Clinical Global Impression Scale

The Clinical Global Impression (CGI) scale was used to measure illness severity, global improvement or change and therapeutic response. The CGI is completed by the researcher at each visit. The questionnaire consists of three questions, two are on a seven-point scale, with the severity of illness scale using a range of responses from one (normal) through to seven (among the most severely ill patients) (Busner & Targum, 2007). The CGI measure has been utilised in similar populations to determine changes in child and adolescent behaviour (Farmer & Aman, 2013).

Procedure

Advertisements were placed on social media, in local newsletters and newspapers, and promoted on local television. Families from the state of Victoria in Australia contacted Swinburne University of Technology if they were interested in enrolling their child in the study. Researchers conducted a phone screen with parents or guardians of the children to determine their child's eligibility. If eligible, families attended the university and completed informed consent forms (both child and parent/guardian) before undertaking further screening. Researchers administered the WISC-IV short form to determine the child's IQ. Any child with an IQ over 80 was eligible to take part. Parents also completed the structured ADHD DSM-IV rating scale. If the parent or guardians rating of the child's symptoms met eligibility criteria (>15 points), the child was officially eligible for the study. The participant completed practice sessions of the CNS-VS, Jensen Box, and CDI. Parents completed the CPRS, current health and medical questionnaire, a demographics questionnaire, and the PSPSI. At the conclusion of the practice and screening session, parents were given one weeks' worth of treatment (placebo) as well as a treatment diary to complete daily. A baseline testing session was scheduled for the same day and time the following week. At baseline (Visit 2), participants completed the CNS-VS, CDI, and Jensen Box, while parents completed the CPRS, the PSPSI and researchers completed the health and medical check and the CGI. At the conclusion of the baseline session, parents were provided with 7 weeks of treatment and a new treatment diary with instructions to return all treatment bottles and diaries at next visit. All testing was repeated at Visit 3 and 4. At Visit 4, once testing had concluded, parents were once again provided with one weeks' treatment (placebo) and another treatment diary. One week later, at Visit 5 (Week 16) parents handed in any remaining treatment, bottles, and diaries, and were reimbursed with a \$50 cheque to assist with travel costs for attending the sessions, while participants were provided with a \$50 book voucher and 3-months' supply of the CDRI 08[®] treatment.

Data Analyses

All analyses were computed using the *Statistical Package for the Social Sciences (SPSS)* version 24 (IBM, 2016) and completed before unblinding. Time by treatment analyses were conducted across all variables utilising a repeated measure analysis of covariance (ANCOVA) design with Bonferroni correction (baseline scores as covariates). Bonferroni correction was used to correct p -values for multiple comparisons, increasing the chance of avoiding a type-I error (Armstrong, 2014). All baseline means and standard deviations presented in tables below were derived from independent samples t -tests. All baseline scores were subjected to paired samples t -test design to determine any differences between treatment groups. Effect sizes were calculated using Cohen's d and were based on within group changes between baseline and week 8, and baseline and week 15. Significant findings were set at $p < 0.05$.

Results

One hundred and twelve participants (CDRI 08[®] $n = 56$) were recruited into a randomised, double-blind, placebo-controlled, parallel groups intervention trial at Swinburne University of Technology in Melbourne. Average age of the participants was 8.8 years. Eighty-two participants completed the trial (CDRI 08[®] $n = 37$), with thirty participants dropping out (CDRI 08[®] $n = 19$). Eleven of these participants dropped out mid trial (CDRI 08[®] $n = 9$), meaning their data was valid for use in an intention-to-treat last observation carried forward (ITT-LOCF) data analysis. Only two participants failed to meet eligibility criteria at the practice/screening visit following successful phone screens.

Demographic information highlighted no significant differences in height, weight, school year level, ethnicity, parental marital status, handedness, eye correction, or special diet (see Table 3). There was a significant difference between groups in those who were consuming additional supplements, however, when these are broken down into supplement type (children's multivitamin, fish oil, melatonin, probiotic, or vitamin c) there were no differences in supplement type use between CDRI 08[®] and placebo groups ($F(1,45)=5.51, p=0.09$).

--- Figure 1 here---

---Table 3 here---

Primary outcome variable

Conners' Parent Rating Scales

Effects of CDRI 08[®] in male children

At V2, following seven days of placebo treatment, the CPRS was completed by parents again. There was no significant difference between treatment groups at baseline on the CPRS outcome variable. Table 4 outlines the outcomes on the CPRS at baseline between the two treatment groups. In a repeated measure ANCOVA with bonferroni correction and baseline scores as covariates, one trending toward significance result indicated an increase in parental perceptions of aggression symptoms in children consuming CDRI 08[®] at V3 compared to placebo ($F(1, 85) = 3.97, p = .05$), but not at study end ($F(1, 85) = 0.45, p = .50$).

--- Table 4 about here---

Secondary outcome variables

CNS Vital Signs

The current study data indicated no significant differences at baseline between treatment groups on the CNS-VS cognitive test. Repeated measures ANCOVAs with bonferroni correction, with baseline values as covariates, demonstrated a significant decrease in errors of commission on the ST for those taking CDRI 08[®] at V4 ($F(1, 76) = 4.34, p = .04$), and a significant decrease in ST reaction time for those taking placebo ($F(1, 76) = 4.49, p = .04$). There were also significant findings at V3 between treatment groups. Children consuming CDRI 08[®] demonstrated an increase in cognitive flexibility at V3 ($F(1, 78) = 7.90, p = .01$), and executive functioning at V3 ($F(1, 78) = 7.83, p = .01$), neither were maintained at V4 (see Table 5). Several outcomes demonstrated a trend towards significance, including improvements in processing speed for those taking CDRI 08[®] at V3 ($F(1, 78) = 3.31, p = .07$) as well as a reduction in SAT errors in the CDRI 08[®] group at V3 ($F(1, 78) = 3.58, p = .06$). There was also a reduced left FTT speed for those taking CDRI 08[®] at V4 ($F(1, 76) = 2.92, p = .09$).

--- Table 5 about here---

Pediatric Symptom Checklist

At the conclusion of the cognitive measure, parents of each participant completed a *Pediatric Symptom Checklist* as part of the CNS-VS program (Jellinek, Murphy, & Burns, 1986). This form is a validated measure of psychosocial problems in childhood. It is a 35-item questionnaire that assesses a broad range of attention, externalizing, and internalizing problems. The results demonstrated a trend towards significance in reduction in conduct disorder symptoms in children consuming CDRI 08[®] compared to placebo at V4 ($F(1, 78) = 4.11, p = .05$) (see Table 6).

--- Table 6 about here---

The Hicks Reaction Time Paradigm (Jensen Box)

The Hicks Reaction Time Paradigm (Jensen's Box) separates a participant's decision time (DT) and movement time (MT) from their overall RT. There were no significant differences in DT or MT between treatment groups at baseline or at study end (see Table 7).

--- Table 7 about here---

Children's Depression Inventory

There were no significant differences between treatment groups at baseline on the CDI. Repeated measures ANCOVAs with bonferroni correction, with baseline values as covariates, demonstrated no significant differences between treatment groups at V4 (see Table 8). There was a significant finding at V3 for improved interpersonal problems for children consuming CDRI 08® ($F(1, 74) = 6.09, p = .02$). This finding demonstrated a moderate effect size at V3 and V4, indicating this improvement was persistent until study end, despite the lack of significant differences between treatment groups. There was also a trend towards significance at V3 for feelings of ineffectiveness ($F(1, 74) = 3.94, p = .05$), and total CDI scores in those children consuming CDRI 08® ($F(1, 79) = 3.52, p = .06$).

--- Table 8 about here---

Paediatric Sleep Problem Survey Instrument

Baseline scores revealed no significant differences between treatment groups on the Paediatric Sleep Problem Survey (see Table 9). In the current study, there was a significant improvement in sleep routine in children consuming CDRI 08® at V3 ($F(1, 73) = 4.40, p = .04$). The effect size for sleep routine was well maintained until V4, however, the result was non-significant between treatment groups ($F(1, 73) = 1.33, p = .25$). No further significant outcomes were noted at V3 or V4.

--- Table 9 about here---

Clinical Global Impression

The *Clinical Global Impression* scale (CGI) is completed by researchers at each visit, providing their view of the participant's level of improvement following each testing session. The third question is the efficacy index, comparing the therapeutic effect (unchanged, minimal, moderate, marked) versus the side effects of the treatment (none, does not interfere with functioning, significantly

interferes with functioning, outweighs therapeutic effect). The first assessment of the child's illness was conducted at V2. Therefore, without treatment, there is no way to assess global improvement or efficacy of treatment. No significant differences were noted at baseline or at any time point during the study.

Placebo run-in and run-out phases

The trial incorporated a placebo run-in and run-out phase in order to reduce any placebo effect that may be seen in parental ratings of their child's behaviour. Changes between visits 1 and 2 may indicate the level of placebo effect, whereas changes between visits 4 and 5 may indicate prolonged treatment effects in the active treatment group, or a reversal of improved cognitive, behavioural, mood and sleep symptoms.

Placebo run-in phase

Mean change and standard deviation scores were calculated between visit 1 and visit 2 on the *Global Index* scores of the CPRS (C. Keith Conners et al., 2011). Those parents or guardians rating the child's behaviour as improved greater than or equal the standard deviation of the mean change on this factor, were removed from analysis ($n = 9$; CDRI 08® $n = 2$). In a separate time by treatment ANCOVA analysis, over three time points (V2, V3, V4) with baseline scores as a covariate and using a bonferroni correction, children consuming CDRI 08® ($n = 40$) demonstrated a trend toward significance for improved peer relations ($F(1,76) = 3.70, p = .06$) over placebo ($n = 39$) as well as an increase in symptoms of aggression ($F(1, 76) = 3.67, p = .06$). No other improvements were noted after factoring in placebo effect changes for behavioural outcomes.

Placebo run-out phase

Between V4 and V 5, all participants were removed from their randomised treatment and consumed placebo for the final week. At V5, participants completed all cognitive and behavioural testing. To determine the effects of treatment change, analysis was conducted using a repeated measures ANCOVA with V4 scores as a covariate and bonferroni correction. One significant finding was noted on the CNS-VS cognitive measure denoted as the *neurocognitive index* – an average of five domain scores: Composite Memory, Psychomotor Speed, Reaction Time, Complex Attention, and Cognitive Flexibility; representing a global score of neurocognition. Participants consuming CDRI 08® demonstrated a significant drop in their neurocognitive index (NCI) scores following a week of treatment cessation ($F(1,60) = 4.53, p = .04$). A trend toward significance was noted on

Effects of CDRI 08[®] in male children

the *oppositional defiant disorder* scale between visits 4 and 5. Those participants taking CDRI 08[®] demonstrated reduced symptoms of oppositional defiance following a week of treatment cessation ($F(1,77) = 3.44, p = .07$).

Adverse events

Twenty-nine adverse events were reported (CDRI 08[®] n = 14) and attended to by the research project's medical physician, with majority linked to unrelated illnesses (cold and flu n = 6; CDRI 08[®] n = 2). Several cases reported gastrointestinal discomfort (CDRI 08[®] n = 3), a common side effect of the active treatment; these cases were short-lived, with each of these participants continuing in the study.

Discussion

The current study examined the efficacy of Bacopa monnieri (BM; CDRI 08[®]), on the symptoms of attention and behaviour against placebo, in a 14-week randomised, double-blind, placebo-controlled, parallel groups clinical trial. No significant improvements on the primary behavioural outcome (CPRS: parental ratings of ADHD symptomatology) were observed. Improvements in secondary outcomes, however, provide interesting discussion points for consideration. Study outcomes are discussed in relation to ADHD research and BM intervention trials.

Behavioural outcomes

The present study reported a trend toward significance between treatment groups on the Conners' parent rating scale (CPRS), which indicated an increase in symptoms of aggression in those taking CDRI 08[®] at treatment mid-point (V3). Despite this, the parent-rated paediatric symptoms checklist (PSC) (Jellinek, Bishop, Murphy, Biederman, & Rosenbaum, 1991) indicated a trend towards significance in improved conduct disorder symptoms in children taking CDRI 08[®] at treatment end-point (V4). This is one of the first indicators that CDRI 08[®] may influence psychosocial conduct in children exhibiting symptoms of ADHD. This outcome would need further exploration to determine what effect CDRI 08[®] may have on these behavioural domains. Another conceptually similar behavioural outcome was the Clinical Global Impression scales (CGI) (Busner & Targum, 2007), which demonstrated no significant changes throughout the study.

Behavioural data is vital to child and adolescent research and remains dependent on the observations and insights of parents, guardians, and clinicians. As such, it does require careful interpretation. As in similar research designs, these findings may be impacted by the accuracy and consistency of parent or guardian reports of a child's behaviour. To account for this potential impact,

Effects of CDRI 08[®] in male children

between week 1 and week 2, all participants consumed placebo. This was included to determine any perceived improvements in the child's behaviour from the perspective of the parent or guardian. In the current trial, based on CPRS scores, nine parents/guardians reported improvements in the child's behaviour during the placebo run-in phase. The differences in the outcomes following removal of these datasets, were minimal. Future studies utilising parent-reported outcomes should be cautious when interpreting parent/guardian observational data, given the potential variability and accuracy of ratings.

Cognitive outcomes

Children consuming CDRI 08[®] significantly improved in errors of commission and demonstrated a stable reaction time speed on the Stroop test (ST) at V4 (Gualtieri & Johnson, 2006). Those consuming placebo recorded decreased reaction times on the same task at V4. The current findings may highlight a speed-accuracy trade-off in the placebo condition, indicating that those demonstrating faster reaction times, have done so at a cost of accuracy. Alternatively, these speed-accuracy trade-offs may have been attenuated by consumption of CDRI 08[®] (Mulder et al., 2010). This premise is supported by the reduced number of errors in the CDRI 08[®] group at V3 on the shifting attention test of the CNS-VS. This reduction demonstrated an increased ability to process information correctly and accurately. Further support comes from demonstrated improvements in improved processing speed in those consuming CDRI 08[®] compared to placebo at V3.

The processing speed domain of the CNS-VS explores a child's ability to attend to incoming information and through improved recognition skills, process that information using motor coordination and visuo-perceptual abilities (Gualtieri & Johnson, 2006). Previous research by Stough et al., (2008; 2001) reported improved outcomes in visual information processing following 12 weeks of CDRI 08[®] consumption in healthy adults. Improvements in the domains of cognitive flexibility and executive function were noted in children consuming CDRI 08[®]. Improved cognitive flexibility reflects a child's ability to adapt to rapidly changing and increasingly complex instruction, as well as their ability to reason, control impulses, form strategies, and make decisions (Gualtieri & Johnson, 2006). The current study utilised Cohen's *d* effect sizes to demonstrate the improvements in each group between V2 to V3 and V2 to V4 (Cohen, 1988). The cognitive flexibility domain demonstrated a moderate effect size at V3 ($d = 0.39$) with significant improvements compared to placebo. The magnitude of this effect increased at V4, although the group differences ($d = 0.45$) did not reach significance. The executive function domain effect size between V3 and V4 remained small, though this difference did increase over time ($d = 0.05$; $d = 0.14$ respectively). These improvements in cognitive outcomes are consistent with previous research highlighting improved cognitive

Effects of CDRI 08[®] in male children

performance following the consumption of CDRI 08[®] in healthy adults over the same chronic (3-month) intervention period (Benson et al., 2014; Downey et al., 2013; Stough et al., 2008).

Two further assessments of neurocognitive functioning were administered in the current study, a cognitive measure known as the Hick's Reaction Paradigm (Jensen Box) was utilised to assess a participant's decision time (DT), movement time (MT), mental speed, and rate of information processing using simple and choice reaction times (Hick, 1952; Hyman, 1953). The CNS Vital Signs (CNS-VS) computerized test battery was further used to assesses visual and verbal memory, reaction time, motor speed, processing speed, simple attention, and executive function. Subtests include verbal memory test (VBM), visual memory test (VIM), finger tapping test (FTT), symbol digit coding (SDC), the Stroop test (ST), shifting attention test (SAT), and a continuous performance test (CPT). Previous research has observed neurocognitive benefits associated with BM consumption [e.g., see meta-analysis by Kongkeaw et al., (2014)], which have been attributed to its anti-oxidant neuroprotective, acetylcholinesterase inhibition, choline acetyltransferase activation, increased cerebral blood flow effects that further modulate neurotransmitter activity. In the current study, the outcomes from the Hick's paradigm and CNS-VS were not significantly impacted by BM consumption. Interestingly, a decrease in neurocognitive performance on the CNS-VS by participants in the CDRI 08[®] group was noted once they were followed up after the treatment period. This finding is particularly intriguing and highlights a need for a more in-depth investigation into the cognitive changes in children and adolescents consuming CDRI 08[®].

Mood outcomes

Past research has highlighted an improvement in mood scores in adults taking BM in acute settings (Benson et al., 2014), but not consistently in chronic settings (Calabrese et al., 2008). The current study utilised the Children's Depression Inventory (CDI) to investigate any changes in mood (Kovacs, 1985). Significant improvements in interpersonal problems were noted at V3 in those consuming CDRI 08[®] over placebo. Despite the significant difference between groups not being maintained, the effect size remained moderate in children taking CDRI 08[®] within the interpersonal problems domain, between V3 ($d = 0.49$) and V4 ($d = 0.36$). The trend toward significance in improved feelings of ineffectiveness were moderate at V3 ($d = 0.52$), decreasing at V4 ($d = 0.41$), and were similar in total CDI scores at V3 ($d = 0.50$) and at V4 ($d = 0.41$). These effect sizes indicate that the reduction in emotional and functional problems persisted for the CDRI 08[®] group, with the placebo group not demonstrating similar changes. Improvements in interpersonal problems and ineffectiveness could be viewed as being complementary, with the prior indicating an improved ability of the child to interact with their peers, as well improved feelings of loneliness within the family unit, and the latter

Effects of CDRI 08® in male children

indicating an improved evaluation of one's own abilities, academic performance, and their capacity to enjoy school and other activities (Bae, 2012). These outcomes are particularly pertinent to the group of children in the study, as the age range encapsulates those children trying to navigate the complexities of school, family, and social life.

Sleep outcomes

The results of the current study indicated an improved sleep routine between V2 and V3 in children consuming CDRI 08® over placebo (Biggs et al., 2012). This finding was not maintained at V4. The effect size analysis indicates these improvements were moderate and somewhat maintained from V3 ($d = 0.52$) until study end (V4) ($d = 0.33$). This improvement highlights a symptom commonly associated with ADHD, in sleep problems (Mayes et al., 2008). When addressed, improved sleep problems may positively impact the cognitive and mood management of ADHD sufferers. The impact of BM supplementation upon the bidirectional relationship of sleep (quality, duration) and mood management is certainly worthy of further investigation.

Limitations

Attrition rates throughout the study may have had a significant impact on outcome data in the current study (see Fig. 1). There were 19 dropouts between visits 2- and 3-, with an average compliance of 83% for those still in the study. There were 11 dropouts between visits 3 and 4 with an average compliance of 84% for participants still in the study. A-priori calculations for a repeated measures design with 2-groups (treatment vs placebo) and 3-time points (2 weeks, 8 weeks, 15 weeks) determined that there would be an 80% chance of discovering a medium effect size difference ($d=0.5$) between treatment groups with a total sample size of 86 participants (alpha level = 0.05). Furthermore, it was determined that there would be an 80% chance of discovering a medium effect size ($d=0.5$) interaction between treatment group and time points with a total sample size of only 40 participants (alpha level = 0.01). With two groups of 25 participants, the study was adequately powered (72%) to detect small changes in the primary outcome measure, the CPRS. Therefore, attrition in the current study most likely did not affect behavioural outcome measures.

In terms of cognitive outcomes, the current study recruited a significantly larger sample size compared to previous child studies ($n= 40, 28, 36, 31$) (Asthana et al., 2001; U.P. Dave et al., 2008; Negi et al., 2000; Sharma et al., 1987), despite this, the attrition rates may have impacted the statistical power of cognitive outcomes at V4 (study end). Controlling for placebo effects also remains an issue in child and adolescent intervention trials. In the current trial, nine parents reported improvements in their child despite being on a placebo during the first week of the trial.

Effects of CDRI 08[®] in male children

Re-analysis of the parent-reported behavioural data with these nine participants removed, revealed no significant outcomes between treatment groups. One confounding role may have been the physical activity of the participants throughout the trial. This was not measured in the current trial and would benefit future trials to include such outcomes.

Conclusion

The current study did not confirm the primary hypothesis that 14-week administration of CDRI 08[®] would reduce symptoms of ADHD. Extracts of Bacopa have previously demonstrated an increased improvement in memory, with significant improvements in free recall (Barbhaiya et al., 2008; Calabrese et al., 2008; Morgan & Stevens, 2010; Stough et al., 2001) and associative memory (Barbhaiya et al., 2008; Roodenrys et al., 2002). Our results are more closely aligned with previous studies showing improved processing speed and cognitive flexibility in healthy young adults (Stough et al., 2001). Systematic reviews have also reported evidence for BM as a cognitive enhancer in child and adolescent populations (Kean et al., 2016; Kean, Downey, & Stough, 2017). Improvements in executive function, cognitive flexibility, and processing speed at V3 support this previous research (Barbhaiya et al., 2008; Calabrese et al., 2008; Morgan & Stevens, 2010; Stough et al., 2001). Improvements in cognition were maintained in those consuming CDRI 08[®] up until V4 (week 15), however, they did not prove statistically significant when compared to placebo. This lack of statistical significance in outcomes at V4 may be due to attrition rates in the first half of the intervention period (n = 19), reducing the statistical power in the latter half of the study. Only 11 participants were able to be used for intention to treat analysis (CDRI 08[®] n = 9), with 19 dropping from the study too early for their data to be used (CDRI 08[®] n = 10).

The current research highlights the potential for families witnessing the negative impact of ADHD symptoms on a family members academic performance, to explore a safe, alternative option to pharmacotherapy. The population of children and adolescents experiencing these symptoms is widespread, making the generalizability of these findings considerably important in this context. The extensive list of associated symptoms that vary in severity, require a safe and successful long-term intervention. The lack of significant improvements in behavioural outcome could highlight the potential for further study into dose-ranging of CDRI 08[®] in a similar population with a more restricted age range and symptom profile. The current study demonstrated that CDRI 08[®] may be beneficial in improving cognitive outcomes in male children aged 6 to 14 years, over 7-weeks of consumption. Further study is warranted to replicate these findings and identify the mechanisms through which the cognitive and behavioural improvements manifest, and whether their longer-term impact moderate's parental ratings of ADHD symptomatology.

Clinical Significance

Effects of CDRI 08® in male children

The current research highlights the benefits of CDRI 08® in domains of cognitive functioning in male children and adolescents exhibiting symptoms of hyperactivity and inattention. Scientifically validated alternatives such as CDRI 08®, provide parents of children with symptoms of ADHD a safe method for treating these symptoms. The clinical significance of the current study is the novel nature of the research itself. No research trial has investigated CDRI 08® in children and adolescents in relation to symptoms of ADHD, making the current study the first to do so.

Financial disclosures

The study was funded by a grant to Prof. C. Stough from Soho Flordis International Australia Pty Ltd.

Conflict of interest

No conflicts of interest to declare.

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Tables & Figures

Table 1. Measures and Visit Schedule

| Behavioural & Demographic Measures | V1 Screening Week 0 | V2 Baseline Week 1 | V3 Follow-up 1 Week 8 | V4 Follow-up 2 Week 15 | V5 Final Visit Week 16 |
|---|---|-----------------------------------|---------------------------------|-------------------------------------|----------------------------------|
| | Administered 1 week dose of placebo to all participants | Administered randomized treatment | Continuing randomized treatment | Administered 1 week placebo run out | Return of any remaining capsules |
| Structured interview (ADHD rating) | X | | | | |
| WISC-IV | X | | | | |
| Conners' Parent Rating Scale | X | X | X | X | X |
| Global Clinical Impression Scale | | X | X | X | |
| Health & Medical Questionnaire | X | X | X | X | X |
| Demographics Questionnaire | X | | | | |

| Cognitive & Mood Measures | | | | | |
|---|---|---|---|---|---|
| CNS Vital Signs (CNSVS) | X | X | X | X | X |
| Hick Reaction Time Paradigm | X | X | X | X | X |
| Child Depression Inventory (CDI) | X | X | X | X | X |
| Paediatric Sleep Problems Survey Instrument (PSPSI) | X | X | X | X | X |

WISC-IV = Wechsler Intelligent Scale for Children 4th Edition

Table 2. CNS-VS multiple test clinical domains

| | |
|----------------------------|---|
| Neurocognitive Index (NCI) | Composite Memory, Psychomotor Speed, Reaction Time, Complex Attention , and Cognitive Flexibility |
| Composite Memory | VBM Correct Hits Immediate + VBM Correct Passes Immediate + VBM Correct Hits Delay + VBM Correct Passes Delay + VIM Correct Hits Immediate + VIM Correct Passes Immediate + VIM Correct Hits Delay + VIM Correct Passes Delay |
| Psychomotor Speed | FTT Right Taps Average + FTT Left Taps Average + SDC Correct Responses |
| Complex Attention | Stroop Commission Errors + SAT Errors + CPT Commission Errors + CPT Omission Errors |
| Cognitive Flexibility | SAT Correct Responses - SAT Errors - Stroop Commission Errors |

CPT = continuous performance test; FTT = finger tapping test; SAT = shifting attention test; SDC = symbol digit coding; VBM = verbal memory; VIM = visual memory.

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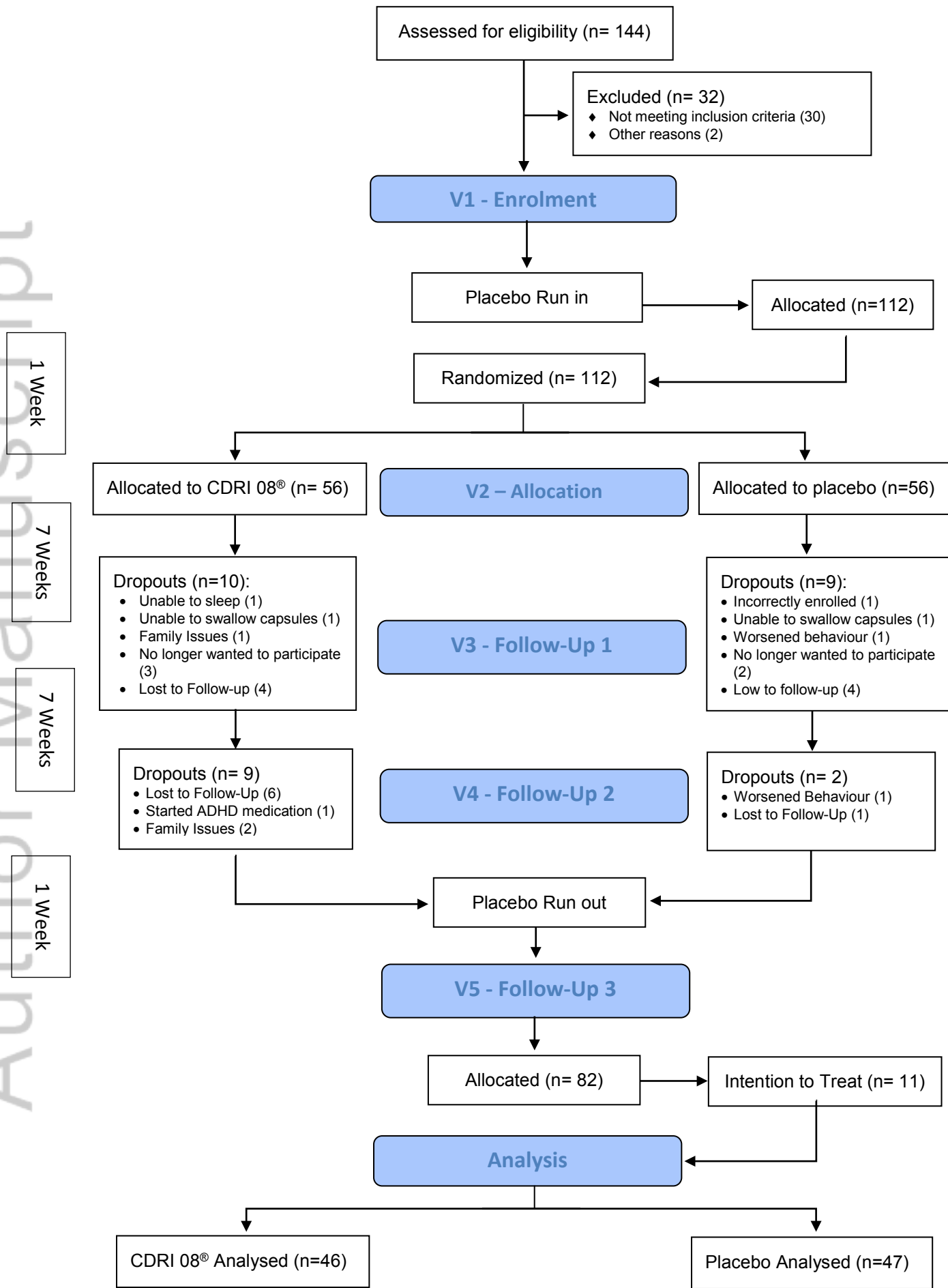


Figure 1. CONSORT 2010 Flow Diagram

Table 3. Demographic information

| | Age | Height (cm) | Weight (kg) | School Year | Parent Married | Parent Single | Parent Status Divorced | Handed (right) | Glasses | Special Diet | Concomitant Medications | WISC-IV Score | DSM ADHD Rating Scale |
|---------|------|-------------|-------------|-------------|----------------|---------------|------------------------|----------------|---------|--------------|-------------------------|---------------|-----------------------|
| CDRI 08 | 8.54 | 137.55 | 35.60 | 3.07 | 64.29% | 14.29% | 12.50% | 76.79% | 17.86% | 5.36% | 37.50% | 107.48 | 35.41 |
| Placebo | 9.05 | 136.96 | 37.05 | 3.71 | 53.57% | 19.64% | 16.07% | 82.14% | 10.71% | 14.29% | 23.21% | 107.47 | 33.60 |

Table 4. Conners' Parent Rating Scale (CPRS) T-Score changes over four time-points inclusive of placebo run-in (V1 to V2)

| | | Practice (V1) | | | Baseline (V2) | | | Week 8 (V3) | | | | Week 15 (V4) | | | |
|-------------------------------|----------|---------------|-------|---------|---------------|-------|---------|-------------|-------|---------|----------|--------------|-------|---------|----------|
| | | N | Mean | SD | N | Mean | SD | N | Mean | SD | <i>d</i> | N | Mean | SD | <i>d</i> |
| Hyperactivity | CDRI 08® | 56 | 76.84 | ± 15.53 | 45 | 75.96 | ± 15.76 | 43 | 78.21 | ± 14.43 | 0.15 | 42 | 75.64 | ± 15.14 | 0.02 |
| | Placebo | 56 | 77.80 | ± 14.49 | 46 | 78.26 | ± 14.75 | 47 | 77.60 | ± 12.70 | 0.05 | 47 | 75.91 | ± 13.88 | 0.16 |
| Inattention | CDRI 08® | 56 | 80.16 | ± 9.96 | 45 | 79.38 | ± 11.06 | 43 | 78.14 | ± 12.62 | 0.10 | 42 | 76.33 | ± 12.66 | 0.26 |
| | Placebo | 56 | 80.55 | ± 10.36 | 46 | 80.33 | ± 9.09 | 47 | 76.36 | ± 10.72 | 0.40 | 47 | 75.34 | ± 12.35 | 0.46 |
| Learning Problems | CDRI 08® | 56 | 63.04 | ± 12.28 | 45 | 61.49 | ± 12.46 | 43 | 61.28 | ± 12.85 | 0.02 | 42 | 60.29 | ± 12.20 | 0.10 |
| | Placebo | 56 | 61.73 | ± 11.59 | 46 | 62.13 | ± 10.51 | 47 | 60.36 | ± 10.64 | 0.17 | 47 | 60.70 | ± 10.81 | 0.13 |
| Executive Function | CDRI 08® | 56 | 67.89 | ± 11.46 | 45 | 68.02 | ± 9.97 | 43 | 66.37 | ± 10.56 | 0.16 | 42 | 66.36 | ± 10.69 | 0.16 |
| | Placebo | 56 | 69.95 | ± 12.30 | 46 | 71.67 | ± 10.44 | 47 | 68.09 | ± 10.86 | 0.34 | 47 | 67.32 | ± 12.71 | 0.37 |
| Peer Relations | CDRI 08® | 56 | 71.25 | ± 14.09 | 45 | 71.40 | ± 12.10 | 43 | 68.56 | ± 10.90 | 0.25 | 42 | 68.62 | ± 11.14 | 0.24 |
| | Placebo | 56 | 70.43 | ± 12.46 | 46 | 71.46 | ± 12.19 | 47 | 68.23 | ± 12.13 | 0.26 | 47 | 70.60 | ± 11.49 | 0.07 |
| Aggression | CDRI 08® | 56 | 80.02 | ± 14.45 | 45 | 76.36 | ± 16.38 | 43 | 79.28 | ± 14.04 | 0.19 | 42 | 76.07 | ± 13.51 | 0.02 |
| | Placebo | 56 | 81.79 | ± 12.39 | 46 | 79.96 | ± 14.65 | 47 | 77.68 | ± 15.89 | 0.15 | 47 | 76.15 | ± 14.60 | 0.26 |
| Global ADHD Index | CDRI 08® | 56 | 77.05 | ± 11.68 | 45 | 75.60 | ± 12.79 | 43 | 73.81 | ± 13.33 | 0.14 | 42 | 72.48 | ± 12.82 | 0.24 |
| | Placebo | 56 | 78.80 | ± 10.27 | 46 | 77.50 | ± 10.43 | 47 | 74.04 | ± 12.19 | 0.30 | 47 | 74.00 | ± 12.79 | 0.30 |
| DSM Hyperactivity | CDRI 08® | 56 | 80.30 | ± 10.19 | 45 | 79.33 | ± 11.12 | 43 | 77.65 | ± 12.74 | 0.14 | 42 | 76.17 | ± 12.29 | 0.27 |
| | Placebo | 56 | 80.23 | ± 11.14 | 46 | 81.17 | ± 9.56 | 47 | 76.64 | ± 11.00 | 0.44 | 47 | 75.89 | ± 13.06 | 0.46 |
| DSM Inattention | CDRI 08® | 56 | 76.68 | ± 13.44 | 45 | 74.93 | ± 14.68 | 43 | 77.63 | ± 12.58 | 0.20 | 42 | 73.83 | ± 14.62 | 0.08 |
| | Placebo | 56 | 76.16 | ± 14.16 | 46 | 77.85 | ± 13.15 | 47 | 76.74 | ± 11.71 | 0.09 | 47 | 74.34 | ± 13.92 | 0.26 |
| Conduct Disorder | CDRI 08® | 56 | 67.50 | ± 14.66 | 45 | 63.20 | ± 12.76 | 43 | 65.49 | ± 14.00 | 0.17 | 42 | 63.60 | ± 14.11 | 0.03 |
| | Placebo | 56 | 69.14 | ± 14.55 | 46 | 69.02 | ± 14.39 | 47 | 66.62 | ± 14.82 | 0.16 | 47 | 65.36 | ± 13.99 | 0.26 |
| Oppositional Defiant Disorder | CDRI 08® | 56 | 72.88 | ± 13.91 | 45 | 71.93 | ± 13.58 | 43 | 71.60 | ± 12.72 | 0.02 | 42 | 69.55 | ± 13.14 | 0.18 |
| | Placebo | 56 | 75.29 | ± 12.43 | 46 | 72.87 | ± 13.96 | 47 | 71.38 | ± 14.29 | 0.11 | 47 | 70.49 | ± 14.33 | 0.17 |
| Impaired School Life | CDRI 08® | 56 | 2.02 | ± 1.02 | 45 | 1.89 | ± 0.98 | 42 | 1.88 | ± 0.94 | 0.01 | 38 | 1.68 | ± 0.96 | 0.22 |
| | Placebo | 56 | 2.14 | ± 0.98 | 47 | 2.17 | ± 0.94 | 44 | 1.93 | ± 0.93 | 0.26 | 46 | 1.70 | ± 1.03 | 0.48 |
| Impaired Relationships | CDRI 08® | 56 | 1.66 | ± 1.01 | 45 | 1.44 | ± 0.89 | 41 | 1.41 | ± 0.97 | 0.03 | 38 | 1.16 | ± 0.79 | 0.33 |
| | Placebo | 56 | 1.57 | ± 0.99 | 47 | 1.53 | ± 1.04 | 45 | 1.33 | ± 0.98 | 0.20 | 46 | 1.30 | ± 0.96 | 0.23 |
| Impaired Home Life | CDRI 08® | 56 | 1.88 | ± 0.76 | 44 | 1.80 | ± 0.77 | 41 | 1.49 | ± 0.90 | 0.37 | 36 | 1.31 | ± 0.71 | 0.66 |
| | Placebo | 56 | 1.88 | ± 0.90 | 46 | 1.83 | ± 0.95 | 44 | 1.61 | ± 0.87 | 0.24 | 45 | 1.58 | ± 0.94 | 0.26 |

Data at V2, V3, & V4 includes only completer data (n=93); Significant difference ($p < 0.05$) in bold; trending towards significance in italics; *d* = Cohen's *d* effect size.

Table 5. CNS Vital Signs percentile changes over three time-points

| | | Baseline (V2) | | | Week 8 (V3) | | | | Week 15 (V4) | | | |
|-----------------------|----------|---------------|-------|---------|-------------|--------------|----------------|-------------|--------------|-------|---------|-------------|
| | | N | Mean | SD | N | Mean | SD | <i>d</i> | N | Mean | SD | <i>d</i> |
| Multiple Test Domain | | | | | | | | | | | | |
| Neurocognitive Index | CDRI 08® | 44 | 14.64 | ± 23.62 | 40 | 15.80 | ± 22.55 | 0.05 | 40 | 17.23 | ± 24.11 | 0.11 |
| | Placebo | 44 | 19.50 | ± 23.76 | 46 | 17.30 | ± 23.40 | 0.09 | 45 | 19.84 | ± 25.74 | 0.01 |
| Composite Memory | CDRI 08® | 44 | 11.93 | ± 23.72 | 40 | 9.63 | ± 19.12 | 0.11 | 40 | 10.50 | ± 19.33 | 0.07 |
| | Placebo | 44 | 14.41 | ± 25.17 | 46 | 15.96 | ± 25.45 | 0.06 | 45 | 15.49 | ± 26.30 | 0.04 |
| Psychomotor Speed | CDRI 08® | 44 | 16.32 | ± 25.19 | 40 | 13.20 | ± 19.45 | 0.14 | 40 | 14.65 | ± 21.14 | 0.07 |
| | Placebo | 44 | 19.32 | ± 27.46 | 46 | 16.61 | ± 25.76 | 0.10 | 45 | 21.51 | ± 30.43 | 0.08 |
| Complex Attention | CDRI 08® | 44 | 21.77 | ± 25.69 | 40 | 28.68 | ± 32.74 | 0.24 | 40 | 27.40 | ± 33.10 | 0.19 |
| | Placebo | 44 | 27.66 | ± 27.80 | 46 | 24.96 | ± 26.00 | 0.10 | 45 | 30.11 | ± 31.25 | 0.08 |
| Cognitive Flexibility | CDRI 08® | 44 | 28.95 | ± 29.46 | 40 | 41.05 | ± 33.08 | 0.39 | 40 | 43.58 | ± 35.12 | <u>0.45</u> |
| | Placebo | 44 | 37.20 | ± 32.71 | 46 | 35.24 | ± 30.45 | 0.06 | 45 | 44.96 | ± 33.12 | 0.24 |
| Single Test Domain | | | | | | | | | | | | |
| Verbal Memory | CDRI 08® | 44 | 29.70 | ± 28.77 | 40 | 34.60 | ± 31.75 | 0.16 | 40 | 36.43 | ± 34.11 | 0.21 |
| | Placebo | 44 | 30.55 | ± 28.98 | 46 | 29.98 | ± 27.23 | 0.02 | 45 | 34.91 | ± 28.95 | 0.15 |
| Visual Memory | CDRI 08® | 44 | 32.18 | ± 32.61 | 40 | 33.60 | ± 32.31 | 0.04 | 40 | 34.75 | ± 33.83 | 0.08 |
| | Placebo | 44 | 32.55 | ± 28.26 | 46 | 38.09 | ± 33.59 | 0.18 | 45 | 43.64 | ± 32.31 | 0.37 |
| Reaction Time | CDRI 08® | 44 | 23.34 | ± 29.07 | 40 | 35.05 | ± 32.04 | 0.38 | 40 | 37.63 | ± 35.34 | 0.44 |
| | Placebo | 44 | 32.59 | ± 31.91 | 46 | 30.20 | ± 30.08 | 0.08 | 45 | 36.76 | ± 34.20 | 0.13 |
| Processing Speed | CDRI 08® | 44 | 14.73 | ± 25.86 | 40 | <i>12.93</i> | ± <i>23.45</i> | 0.07 | 40 | 16.78 | ± 26.73 | 0.08 |
| | Placebo | 44 | 18.48 | ± 27.65 | 46 | 21.54 | ± 28.73 | 0.11 | 45 | 21.18 | ± 30.72 | 0.09 |
| Executive Function | CDRI 08® | 44 | 16.25 | ± 26.59 | 40 | 15.00 | ± 25.19 | 0.05 | 40 | 13.05 | ± 19.80 | <u>0.14</u> |
| | Placebo | 44 | 16.95 | ± 24.95 | 46 | 18.89 | ± 25.12 | 0.08 | 45 | 18.80 | ± 28.56 | 0.07 |
| Simple Attention | CDRI 08® | 44 | 15.09 | ± 25.34 | 40 | 10.03 | ± 19.68 | 0.22 | 40 | 8.00 | ± 16.24 | 0.33 |
| | Placebo | 44 | 15.07 | ± 22.79 | 46 | 12.63 | ± 22.37 | 0.11 | 45 | 11.56 | ± 20.93 | 0.16 |
| Motor Speed | CDRI 08® | 44 | 37.36 | ± 31.15 | 40 | 40.55 | ± 30.37 | 0.10 | 40 | 41.85 | ± 32.81 | 0.14 |
| | Placebo | 44 | 36.75 | ± 27.92 | 46 | 35.26 | ± 27.96 | 0.05 | 45 | 39.53 | ± 28.33 | 0.10 |

Significant difference ($p < 0.05$) in bold; trending towards significance in italics; d = Cohen's d effect size

Table 6. Paediatric Symptom Checklist from CNS Vital Signs over three time-points

| | | Baseline (V2) | | | Week 8 (V3) | | | | Week 15 (V4) | | | |
|----------------------|----------------------|---------------|-------|---------|-------------|-------|---------|----------|--------------|-------|---------|----------|
| | | N | Mean | SD | N | Mean | SD | <i>d</i> | N | Mean | SD | <i>d</i> |
| Attention | CDRI 08 [®] | 46 | 6.70 | ± 3.21 | 37 | 7.14 | ± 2.62 | 0.15 | 36 | 7.28 | ± 2.15 | 0.21 |
| | Placebo | 47 | 7.06 | ± 3.32 | 46 | 6.48 | ± 3.38 | 0.17 | 45 | 6.98 | ± 2.72 | 0.03 |
| Anxiety / Depression | CDRI 08 [®] | 46 | 3.43 | ± 2.65 | 37 | 3.38 | ± 2.37 | 0.02 | 36 | 3.56 | ± 2.59 | 0.05 |
| | Placebo | 47 | 2.89 | ± 2.11 | 46 | 2.72 | ± 2.31 | 0.08 | 45 | 3.18 | ± 2.53 | 0.12 |
| Conduct Problems | CDRI 08 [®] | 46 | 4.50 | ± 2.89 | 37 | 4.54 | ± 2.84 | 0.01 | 36 | 4.31 | ± 2.70 | 0.07 |
| | Placebo | 47 | 5.00 | ± 3.60 | 46 | 4.87 | ± 3.44 | 0.04 | 45 | 5.69 | ± 3.73 | 0.19 |
| Overall Score | CDRI 08 [®] | 46 | 25.48 | ± 13.53 | 37 | 26.00 | ± 11.58 | 0.04 | 36 | 2.70 | ± 9.90 | 0.08 |
| | Placebo | 47 | 26.15 | ± 13.71 | 46 | 24.46 | ± 13.92 | 0.12 | 45 | 27.20 | ± 14.11 | 0.08 |

Significant changes in bold ($p < 0.05$); *d* = Cohen's *d* effect size.

Table 7. Decision Time (DT) and Movement Time (MT) scores between treatment groups

| | | Baseline (V2) | | | Week 8 (V3) | | | | Week 15 (V4) | | | |
|-------------|----------------------|---------------|------|--------|-------------|------|--------|----------|--------------|------|--------|----------|
| | | N | Mean | SD | N | Mean | SD | <i>d</i> | N | Mean | SD | <i>d</i> |
| Mean DT | CDRI 08 [®] | 44 | 0.85 | ± 0.48 | 44 | 0.84 | ± 0.35 | 0.02 | 42 | 0.83 | ± 0.38 | 0.06 |
| | Placebo | 47 | 0.72 | ± 0.31 | 46 | 0.72 | ± 0.29 | 0.02 | 46 | 0.78 | ± 0.35 | 0.17 |
| Mean MT | CDRI 08 [®] | 44 | 1.35 | ± 0.74 | 44 | 1.29 | ± 0.58 | 0.09 | 42 | 1.26 | ± 0.58 | 0.13 |
| | Placebo | 47 | 1.12 | ± 0.56 | 46 | 1.10 | ± 0.54 | 0.02 | 46 | 1.15 | ± 0.50 | 0.06 |
| DT Choice-8 | CDRI 08 [®] | 44 | 0.81 | ± 0.34 | 44 | 0.82 | ± 0.34 | 0.03 | 42 | 0.88 | ± 0.48 | 0.15 |
| | Placebo | 47 | 0.71 | ± 0.34 | 46 | 0.77 | ± 0.38 | 0.17 | 46 | 0.85 | ± 0.53 | 0.31 |
| DT Choice-4 | CDRI 08 [®] | 44 | 0.91 | ± 0.67 | 43 | 0.86 | ± 0.43 | 0.08 | 42 | 0.83 | ± 0.43 | 0.14 |
| | Placebo | 47 | 0.74 | ± 0.35 | 46 | 0.74 | ± 0.35 | 0.02 | 46 | 0.81 | ± 0.45 | 0.17 |
| DT Choice-2 | CDRI 08 [®] | 43 | 0.85 | ± 0.55 | 43 | 0.82 | ± 0.40 | 0.05 | 42 | 0.84 | ± 0.57 | 0.01 |
| | Placebo | 45 | 0.74 | ± 0.45 | 45 | 0.70 | ± 0.38 | 0.10 | 46 | 0.79 | ± 0.44 | 0.11 |
| DT Choice-1 | CDRI 08 [®] | 43 | 0.75 | ± 0.48 | 43 | 0.81 | ± 0.51 | 0.12 | 42 | 0.75 | ± 0.41 | 0.00 |
| | Placebo | 44 | 0.67 | ± 0.31 | 44 | 0.65 | ± 0.30 | 0.05 | 44 | 0.67 | ± 0.35 | 0.02 |
| MT Choice-8 | CDRI 08 [®] | 44 | 1.32 | ± 0.63 | 44 | 1.33 | ± 0.58 | 0.01 | 42 | 1.39 | ± 0.70 | 0.11 |
| | Placebo | 47 | 1.16 | ± 0.59 | 46 | 1.18 | ± 0.55 | 0.04 | 46 | 1.23 | ± 0.68 | 0.11 |
| MT Choice-4 | CDRI 08 [®] | 43 | 1.33 | ± 0.75 | 43 | 1.27 | ± 0.58 | 0.09 | 42 | 1.27 | ± 0.65 | 0.08 |
| | Placebo | 47 | 1.13 | ± 0.62 | 46 | 1.12 | ± 0.60 | 0.01 | 46 | 1.23 | ± 0.71 | 0.16 |
| MT Choice-2 | CDRI 08 [®] | 43 | 1.36 | ± 0.92 | 43 | 1.24 | ± 0.64 | 0.16 | 42 | 1.26 | ± 0.79 | 0.12 |
| | Placebo | 45 | 1.12 | ± 0.76 | 45 | 1.08 | ± 0.67 | 0.05 | 46 | 1.15 | ± 0.59 | 0.05 |
| MT Choice-1 | CDRI 08 [®] | 43 | 1.22 | ± 0.77 | 43 | 1.20 | ± 0.72 | 0.02 | 42 | 1.12 | ± 0.55 | 0.15 |
| | Placebo | 44 | 1.01 | ± 0.57 | 44 | 0.99 | ± 0.59 | 0.03 | 44 | 0.99 | ± 0.50 | 0.04 |

Significant changes in bold ($p < 0.05$); d = Cohen's d effect size.

Table 8. Children's Depression Inventory (CDI) T-Score changes over three time-points

| | | Baseline (V2) | | | Week 8 (V3) | | | | Week 15 (V4) | | | |
|------------------------|----------|---------------|-------|---------|-------------|--------------|----------------|-------------|--------------|-------|---------|-------------|
| | | N | Mean | SD | N | Mean | SD | <i>d</i> | N | Mean | SD | <i>d</i> |
| Total Score | CDRI 08® | 44 | 50.57 | ± 11.83 | 41 | 44.07 | ± 14.30 | 0.50 | 38 | 45.29 | ± 14.18 | 0.41 |
| | Placebo | 42 | 46.64 | ± 9.24 | 41 | 48.10 | ± 9.99 | 0.15 | 40 | 46.75 | ± 10.54 | 0.01 |
| Negative Mood | CDRI 08® | 44 | 50.86 | ± 12.78 | 41 | 45.56 | ± 13.44 | 0.40 | 38 | 45.47 | ± 14.91 | 0.39 |
| | Placebo | 42 | 47.38 | ± 9.42 | 41 | 48.59 | ± 10.58 | 0.12 | 40 | 46.30 | ± 9.06 | 0.12 |
| Interpersonal Problems | CDRI 08® | 44 | 53.00 | ± 11.34 | 41 | 46.95 | ± 13.17 | 0.49 | 38 | 48.18 | ± 15.68 | 0.36 |
| | Placebo | 42 | 48.86 | ± 9.31 | 41 | 51.73 | ± 11.28 | 0.28 | 40 | 48.03 | ± 9.31 | 0.09 |
| Ineffectiveness | CDRI 08® | 44 | 50.36 | ± 8.76 | 41 | 44.68 | ± 12.95 | 0.52 | 38 | 45.68 | ± 13.87 | 0.41 |
| | Placebo | 42 | 46.79 | ± 7.85 | 41 | 47.98 | ± 8.67 | 0.14 | 40 | 46.40 | ± 7.10 | 0.05 |
| Anhedonia | CDRI 08® | 44 | 51.25 | ± 11.69 | 41 | 47.39 | ± 15.29 | 0.29 | 38 | 46.63 | ± 15.10 | 0.35 |
| | Placebo | 42 | 48.95 | ± 11.18 | 41 | 50.68 | ± 12.31 | 0.15 | 40 | 48.43 | ± 9.59 | 0.05 |
| Negative Self Esteem | CDRI 08® | 44 | 46.80 | ± 8.93 | 41 | 43.10 | ± 13.00 | 0.33 | 38 | 43.68 | ± 12.96 | 0.28 |
| | Placebo | 42 | 44.57 | ± 5.69 | 41 | 44.10 | ± 4.55 | 0.09 | 40 | 43.88 | ± 5.63 | 0.12 |

Significant changes in bold ($p < 0.05$); d = Cohen's d effect size.

Table 9. Paediatric Sleep Problem Survey Instrument (PSPSI) T-Score changes over three time-points

| | | Baseline (V2) | | | Week 8 (V3) | | | | Week 15 (V4) | | | |
|----------------------------|----------|---------------|-------|---------|-------------|--------------|----------------|-------------|--------------|-------|---------|-------------|
| | | N | Mean | SD | N | Mean | SD | <i>d</i> | N | Mean | SD | <i>d</i> |
| Sleep Routine | CDRI 08® | 44 | 76.30 | ± 6.43 | 41 | 69.41 | ± 17.95 | 0.52 | 38 | 71.92 | ± 18.50 | 0.33 |
| | Placebo | 42 | 74.45 | ± 7.52 | 40 | 74.40 | ± 6.21 | 0.01 | 40 | 74.50 | ± 6.35 | 0.01 |
| Bedtime Anxiety | CDRI 08® | 44 | 62.25 | ± 7.57 | 41 | 59.68 | ± 16.17 | 0.21 | 38 | 58.18 | ± 15.74 | 0.34 |
| | Placebo | 42 | 61.40 | ± 7.16 | 40 | 60.58 | ± 6.26 | 0.12 | 40 | 60.80 | ± 8.20 | 0.08 |
| Morning Tiredness | CDRI 08® | 44 | 54.07 | ± 10.88 | 41 | 54.37 | ± 18.83 | 0.02 | 38 | 50.87 | ± 15.40 | 0.24 |
| | Placebo | 42 | 54.33 | ± 14.03 | 40 | 53.13 | ± 11.44 | 0.09 | 40 | 52.95 | ± 11.59 | 0.11 |
| Night Arousals | CDRI 08® | 44 | 47.05 | ± 7.87 | 41 | 45.34 | ± 13.24 | 0.16 | 38 | 42.84 | ± 11.75 | 0.43 |
| | Placebo | 42 | 47.67 | ± 10.05 | 40 | 48.80 | ± 10.44 | 0.11 | 40 | 45.63 | ± 7.38 | 0.23 |
| Sleep Disordered Breathing | CDRI 08® | 44 | 50.55 | ± 9.21 | 41 | 49.80 | ± 16.41 | 0.06 | 38 | 46.26 | ± 13.90 | 0.37 |
| | Placebo | 42 | 50.64 | ± 10.31 | 40 | 50.35 | ± 10.88 | 0.03 | 40 | 48.80 | ± 8.69 | 0.19 |
| Restless Sleep | CDRI 08® | 44 | 50.36 | ± 11.78 | 41 | 49.56 | ± 16.03 | 0.06 | 38 | 45.50 | ± 15.85 | 0.35 |
| | Placebo | 42 | 50.50 | ± 11.17 | 40 | 47.90 | ± 8.89 | 0.26 | 40 | 46.83 | ± 9.00 | 0.36 |

Significant changes in bold ($p < 0.05$); d = Cohen's d effect size.

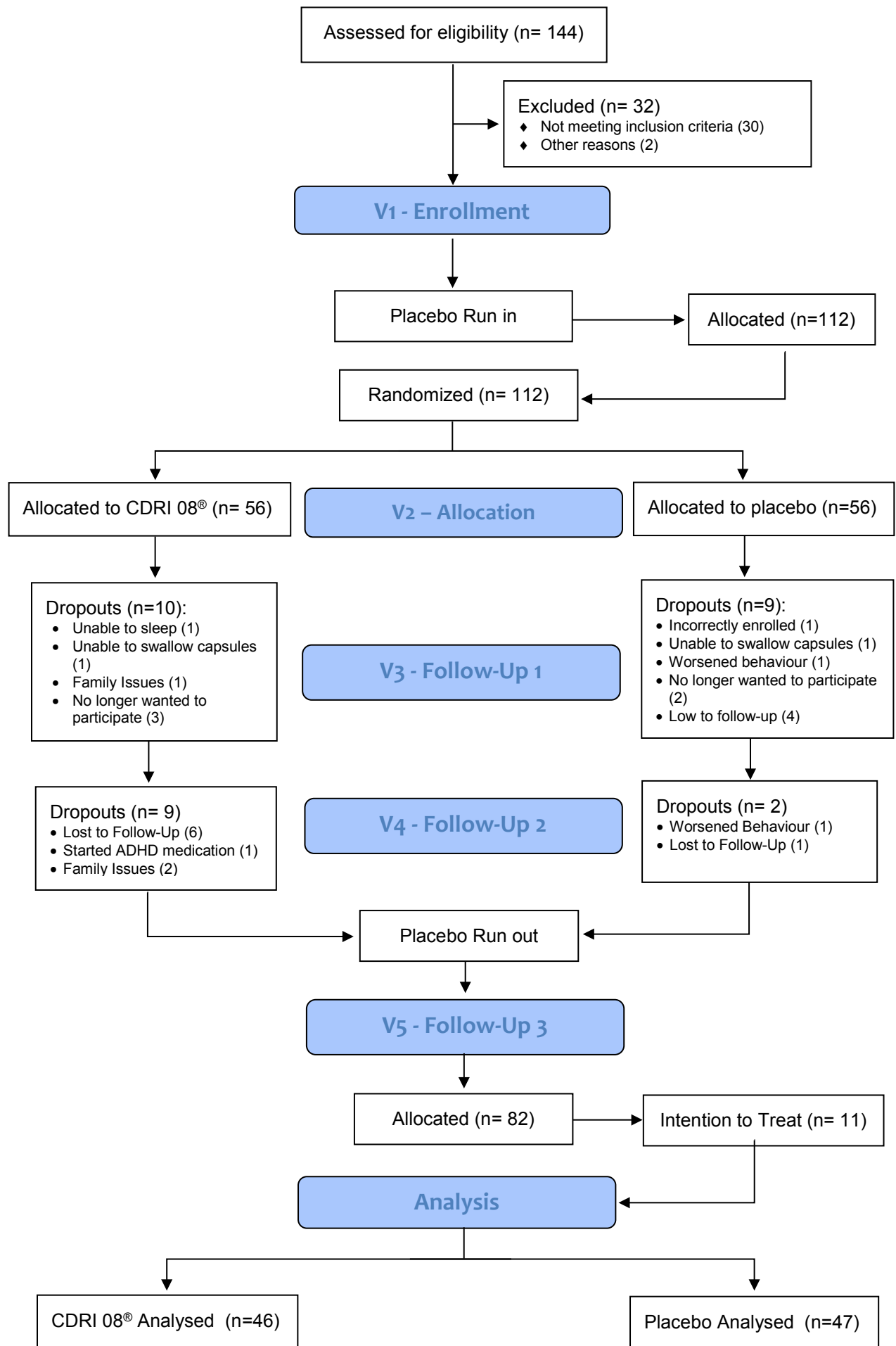


Figure 1. CONSORT 2010 Flow Diagram

1. Include, at the end of the introduction the aim of the paper.
Page 4
2. Report, in the methods, the purity of the compound under investigation (if extracted from plants). If you are investigating an herbal extract, report evidence of chemical characterization.
Page 6
3. Provide the species, strain, sex, weight and source of the animals.
NOT APPLICABLE
4. Provide the source and the passage of cell lines indicated.
NOT APPLICABLE
5. Include a statement on randomization and blinding? No problem if the experiments were not randomized/blinded, just state within your manuscript.
Page 6
6. Report, In the result section, the effect of the vehicle (n, mean±SEM) on the response under study.
Each table includes mean, SD, and cohen's d effect sizes for the **active treatment group**
7. Report, possibly in the graphs/tables, the effect of a positive control on the response under study. If not provided, discuss this limitation.
Each table includes mean, SD, and cohen's d effect sizes for the **control group**
8. Indicate the number of experiments in each figures/tables legend.
Each table contains the time-points for each assessment and the number of participants who successfully completed that test at that time-point.
9. How were the concentrations used in vitro selected? Can you provide evidence that you have not used toxic concentrations? If you have used high concentrations (e.g. > 30 µM), provide a valid scientific justification.
NOT APPLICABLE
10. How were the doses used in vivo selected? Are relevant for human translation? Can you discuss the dose used for possible translation in humans, for example, by using conversion tables available in the literature (Nair AB, Jacob S. A simple practice guide for dose conversion between animals and humans. J Basic Clin Pharm. 2016 Mar;7(2):27-31).
NOT APPLICABLE
11. Discuss the in vivo size of the effect in relation to the disease under evaluation. Is the effect of the compound under evaluation clinically-relevant? What is the size of the effect of clinically-used drugs in the experimental model(s) you are using? Please check the literature and discuss this point

NOT APPLICABLE

12. Did you use the oral route of administration? If not, why? If you have not used the oral route of administration, please discuss the rationale. Please also provide the rationale of the timing and frequency of administration.

We have added this sentence on Page 5:

This daily dose is considered safe and clinically appropriate based on past intervention research and tolerability studies (Brimson et al., 2021).

13. Please indicate clearly if you are using a preventive rather than a curative (therapeutic) protocol. In other words, did you administer the compound before or after the insult causing the experimental disease? Do not use a preventive protocol if the main goal of the disease is to cure rather than to prevent. If you have done so, please discuss this limitation.

See page 5 for inclusion criteria. All participants were required to have an established level of inattention and/or hyperactivity before entering the study.

14. Is the compound (or extract) under investigation safe at the in vivo doses used? Check the literature to see if toxicological data are available. Alternatively, try to provide early safety data. If you are not able to provide such data (and such data are not available in the literature), please explain the reasons and discuss in your paper the lack of toxicity data as a limitation of the study.

The compound is safe with well-established safety and tolerability profile. See point 12 above (page 5 of the manuscript)

15. End the discussion with a conclusion reporting the main results and the significance of the study.

Page 19. Paragraph on clinical significance.

REVIEWER: 1

Comments to the Author

Congratulations on a well presented study.

I only have a few minor queries that should be addressed:

The Bacopa herb formulation - Where was it obtained? Who produced it? Was it standardized/ analysed in anyway to confirm its bacopa content? And Importantly, are any of the authors involved in its production, and marketing?

a. Thank you highlighting this missing information. This information has been added to page 5, first paragraph:

i. *“The CDRI 08® extract was supplied by SFI Health™ and is standardized to contain 55% bacosides (based on UV spectrophotometry). The BM plant is harvested twice a year by hand and is analysed before shipment through taxonomic evaluation, a chemical analysis of the active plant ingredient through spectrophotometry, and high-performance liquid chromatography (HPLC) analysis. None of the researchers were involved in the development, marketing or production of the CDRI 08® extract.”*

2. The manuscript mentions a number of other studies that produced positive results when using bacopa in a clinical setting for various memory/cognitive tests... I feel the authors should also discuss the studies that have shown negative results:

Two examples include;

BACOMIND - One clinical study: Sathyanarayanan, V., Thomas, T., Einöther, S. J., Dobriyal, R., Joshi, M. K., & Krishnamachari, S. (2013). Brahmi for the better? New findings challenging cognition and anti-anxiety effects of Brahmi (*Bacopa monniera*) in healthy adults. *Psychopharmacology*, 227(2), 299–306. <https://doi.org/10.1007/s00213-013-2978-z>

One meta-analysis: Brimson, J.M., Brimson, S., Prasanth, M.I. et al. The effectiveness of *Bacopa monnieri* (Linn.) Wettst. as a nootropic, neuroprotective, or antidepressant supplement: analysis of the available clinical data. *Sci Rep* 11, 596 (2021). <https://doi.org/10.1038/s41598-020-80045-2>

Thank you for highlighting these. We have added information regarding the meta-analysis you have mentioned as evidence of negative outcomes. As this meta-analysis describes the outcomes included in the clinical study you have mentioned, we did not include the single study. Please find the updated paragraph on page 3:

“Conversely, one recent meta-analysis noted a lack of consistent positive outcomes for BM in clinical samples (Brimson et al., 2021). This highlights an intriguing gap in the literature between clinical and non-clinical samples. As such, more rigorous clinical trials are required to substantiate these findings across a broader spectrum of disorder-related symptoms.”

3. Please check the reference section is fully up to date, with the most recent reference information. (some of the references appear to be incomplete or possibly formatted incorrectly) so please give them a check... a few examples are below...

Thank you for noticing these. We have updated those you have listed and corrected any others that did not comply with the APA format, as below:

- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5. Retrieved from <http://dsm.psychiatryonline.org/book.aspx?bookid=556>
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- Barbhaiya, H. C., Desai, R. P., Saxena, V. S., Pravina, K., Wasim, P., Geetharani, P., . . . Amit, A. (2008). Efficacy and tolerability of BacoMind® on memory improvement in elderly participants - A double blind placebo controlled study. *Journal of Pharmacology and Toxicology*, 3(6), 425-434. Retrieved from <http://www.scopus.com/inward/record.url?eid=2-s2.0-63249098562&partnerID=40&md5=ad0bb36b04b77fbc81343b48744cd800>
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- Calabrese, C., Gregory, W. L., Leo, M., Kraemer, D., Bone, K., & Oken, B. (2008). Effects of a standardized Bacopa monnieri extract on cognitive performance, anxiety, and depression in the elderly: A randomized, double-blind, placebo-controlled trial. *Journal of Alternative and Complementary Medicine*, 14(6), 707-713. Retrieved from <http://www.scopus.com/inward/record.url?eid=2-s2.0-49249128360&partnerID=40&md5=ff9c7d83cb5cfe14372b2c210270b22f>
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates, Publishers. ~~Cohen, J. (1988). Statistical Power Analyses for the Behavioral Sciences (Vol. 2). Hillsdale, N.J.: Erlbaum Associates.~~
- Devena, S. E., & Watkins, M. W. (2012). Diagnostic Utility of WISC-IV General Abilities Index and Cognitive Proficiency Index Difference Scores Among Children With ADHD. *Journal of Applied School Psychology*, 28(2), 133-154. Retrieved from <http://www.scopus.com/inward/record.url?eid=2-s2.0-84861628267&partnerID=40&md5=9d54eda68ea70fb607d01f2f80e2902c>

- Kean, J. D., Downey, L. A., & Stough, C. K. (2017). Systematic Overview of Bacopa monnieri (L.) Wettst. Dominant Poly-Herbal Formulas in Children and Adolescents. *Medicines*, 4(4), 86. Retrieved from <http://www.mdpi.com/2305-6320/4/4/86>
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REVIEWER: 2

Comments to the Author

I advise you to extend your study duration and follow up with the patient for a longer time

Thank you for the suggestion. This study data collection was completed in 2016. Unfortunately, we did not include post-study follow-up for these participants.

REVIEWER: 3

Comments to the Author

I do not have major concerns but I would strongly suggest to discuss the effect size found for the various outcomes (p values alone are not enough) in relation to effect sizes for medication. The authors may want to refer to recent evidence synthesis (eg: <https://protect->

au.mimecast.com/s/AZ_-C5QZOxCZPPJL4SxfscH?domain=pubmed.ncbi.nlm.nih.gov) of ADHD medication effect for this discussion

Thank you for providing that resource. The current trial did not permit children or adolescents consuming ADHD medication into the trial.

Effect sizes were calculated for each outcome measure (see tables 5-9). We agree that p-scores alone do not provide enough of a picture, which is why effect sizes were included and discussed in relation to any perceived maintenance effects.

REVIEWER: 4

Comments to the Author

- Some sentences are not clear like “Validated measures verify the presence of clinical levels of hyperactivity, impulsivity, and inattention, however, many children clinically short.”

Thank you for highlighting this. We have carefully adjusted similar sentences to have more clarity:

“Validated ADHD assessments enable clinicians the ability to verify clinical levels of ADHD symptoms including hyperactivity, impulsivity, and inattention. However, despite exhibiting moderate levels of these symptoms, children often fall short of this clinical cut-off ~~Validated measures verify the presence of clinical levels of hyperactivity, impulsivity, and inattention, however, many children clinically short~~ (Selinus et al., 2016), highlighting a ‘sub-clinical’ category of children and adolescents.

Recent research has indicated a prevalence for children falling within this sub-clinical category to be anywhere from 0.8% to 23% of the population (Balázs & Keresztény, 2014).”

Page 3:

“Nutrient and complementary medicine is a rapidly growing area of innovative research. Such alternative treatments are quickly finding a home in modern medicinal journals (Ashton et al., 2021) and clinical settings. ~~Research into alternative therapies has become increasingly more common (Kean, Downey, & Stough, 2016).”~~

“One Eastern medicinal system, Ayurveda, ~~medicinal system~~ contains frequently researched alternatives to current Western options.”

Please check the whole manuscript to revise such sentences.

- Based on a brief literature review in the introduction section, several previous studies have assessed the effects of BM in adults and children. What is the exact difference between the applied intervention in the current study and previous ones?

No previous research has rigorously investigated CDRI08[®] in a sample of children and adolescents with symptoms of ADHD. Previous work has investigated CDRI08[®] in children with a *diagnosis* of ADHD, however, this remains unpublished. Other extracts have also been investigated for their efficacy in varied disorder profiles. This is the first to investigate the effects of CDRI08[®] across a spectrum of behavioural symptoms while measuring the effects on cognition, mood, and sleep.

- Add manufacturer information to the method. Moreover, provide the placebo composition and other available excipients in the supplement.

Thank you. These details have been provided on Page 5:

“The CDRI 08[®] extract was supplied by SFI Health[™] and is standardized to contain 55% bacosides (based on UV spectrophotometry). The BM plant is harvested twice a year by hand and is analysed before shipment through taxonomic evaluation, a chemical analysis of the active plant ingredient through spectrophotometry, and high-performance liquid chromatography (HPLC) analysis. None of the researchers were involved in the development, marketing, or production of the CDRI 08[®] extract.”

The placebo capsule contents are also provided in the same paragraph, describing the contents as *inert plant-based materials*.

- Add baseline characteristics of participants for baseline comparison between two groups (such as supplement use, body weight, and so on).

Thank you for this helpful suggestion. We have added a demographics table and an explanation of the results on page 9:

“Demographic information highlighted no significant differences in height, weight, school year level, ethnicity, parental marital status, handedness, eye correction, or special diet (see Table 1). There was a significant difference between groups in those who were consuming additional supplements, however, when these are broken down into supplement type (children’s multivitamin, fish oil, melatonin, probiotic, or vitamin c) there were no differences in supplement type use between CDRI 08[®] and placebo groups ($F(1,90)=5.51, p=0.09$).”

- Is there any available data for physical activity or dietary intakes of participants? These variables may play a confounding role.

Data involving special diets was collected and is located in the demographics table. The physical activity of the participants was not measured, and as such has been added to the discussion section under limitations for the current study on page 16:

“One confounding role may have been the physical activity of the participants throughout the trial. This was not measured in the current trial and would benefit future trials to include such outcomes.”

- Add sample size formula with a proper reference to the methods section.

Thank you for this note. A paragraph has been added to page 31 of the methods section detailing the power analysis.

“Power Analysis

*Power analysis using G*Power 3.1.2 (Erdfelder, Faul, & Buchner, 1996), determined there would be an 80% chance of discovering a medium effect size ($f=0.25$) between treatment groups with a sample size of 86 participants (α level = 0.05) on the primary outcome, the CPRS. Previous research reported statistical significance when using Bacopa in similar sample sizes (Stough et al., 2008), with child and adolescent studies examining the efficacy of Bacopa using smaller sample sizes ($n= 40, 28, 36, 31$) (Asthana et al., 2001; U.P. Dave et al., 2008; Negi et al., 2000; Sharma et al., 1987). Given this*

is the first known trial of its kind, the sample size was selected on the basis of previous effect sizes from RCTs administering Bacopa.”

- Regarding applied questionnaires in the current study, are they validated for the children population? In addition, provide the scoring system for them in the methods section.

Thank you. These have been added:

Page 6:

“The CPRS is a valid and reliable measure with high test-retest reliability and effective discriminatory power that determines a child’s symptom severity through raw score conversion to t-scores based on their age and gender across a range of symptoms including inattention, hyperactivity, executive function, learning problems, aggression, conduct disorder, oppositional defiant disorder, peer relations, impairments in relationships, school, and home life, a global ADHD, and an ADHD probability score (Conners, Pitkanen, & Rzepa, 2011).”

Page 6:

“Odd numbered questions represent the inattention subscale, while even numbers represent the hyperactivity-impulsivity subscale. The results are described in terms of subscales, total score, and percentile ranks for each score (DuPaul GJ et al., 1998).”

Page 8:

“The questionnaire reports on six subscales including sleep routine, bedtime anxiety, morning tiredness, night arousals, sleep-disordered breathing, and restless sleep. Questions were rated on a four-point Likert scale of Never, Rarely (once per week), Sometimes (2–4 times per week), or Usually (5–7 times per week). Domain scores were garnered through summing all items within each subscale (Biggs et al., 2012).”

Page 8:

“Scores are tabulated by the researcher or clinician, who uses conversion tables based on normative data to convert the total raw scores to t-scores.”

Page 8:

“Normative data was based on U.S. school children between the ages of 7 to 17 (Kovacs, 1985), with follow-up studies exploring its use in children aged 6 to 17 years (Nelson, Politano, Finch, Wendel, & Mayhall, 1987). Scores are tabulated by the researcher or clinician, who uses conversion tables based on normative data to convert the total raw scores to t-scores.”

Page 8:

“The CGI measure has been utilised in similar populations to determine changes in child and adolescent behaviour (Farmer & Aman, 2013).”

- Add underlying mechanisms of the effects of CDRI 08 supplementation on primary and secondary outcomes.

This is a great suggestion, and the following paragraph has been added to page 5 of the manuscript.

“Current research indicates BM promotes neuroprotection, cerebral blood flow, and modulates acetylcholine, dopamine, and serotonin neurotransmitter activity (Aguiar & Borowski, 2013). BM is also reported to inhibit acetylcholinesterase and reduce beta-amyloid formation and accumulation in the brain (Limpeanchob, Jaipan, & Rattanakaruna, 2008). Based on the research into ADHD, and the purported benefits of stimulant and non-stimulant pharmacotherapy (Sofuoglu & Sewell, 2009), the reported mechanisms of action highlight the potential for BM to improve the behavioural, mood, and executive functioning of children and adolescents exhibiting symptoms of ADHD.”

Further commentary is made in relation to these mechanisms in the discussion on page 17:

“Two further assessments of neurocognitive functioning were administered in the current study, a cognitive measure known as the Hick’s Reaction Paradigm (Jensen Box) was utilised to assess a participant’s decision time (DT), movement time (MT), mental speed, and rate of information processing using simple and choice reaction times (Hick, 1952; Hyman, 1953). The CNS Vital Signs (CNS-VS) computerized test battery was further used to assesses visual and verbal memory, reaction time, motor speed, processing speed, simple attention, and executive function. Subtests include verbal memory test (VBM), visual memory test (VIM), finger tapping test (FTT), symbol digit coding (SDC), the Stroop test (ST), shifting attention test (SAT), and a continuous performance test (CPT). Previous research has observed neurocognitive benefits associated with BM consumption [e.g., see meta-analysis by Kongkeaw et al., (2014)], which have been attributed to its anti-oxidant neuroprotective, acetylcholinesterase inhibition, choline acetyltransferase activation, increased cerebral blood flow effects that further modulate neurotransmitter activity. In the current study, the outcomes from the Hick’s paradigm and CNS-VS were not significantly impacted by BM consumption. Interestingly, a decrease in neurocognitive performance on the CNS-VS by participants in the CDRI 08® group was noted once they were followed up after the treatment period. This finding is particularly intriguing and highlights a need for a more in-depth investigation into the cognitive changes in children and adolescents consuming CDRI 08®.”

- Add the statistically significant level to the statistical analysis section. Accordingly, only present the significant finding in the results section and discuss significant results based on this value.

This has been added to page 9:

“Significant findings were set at $p < 0.05$.”

- In the results section, the authors said that “a significant decrease in ST reaction time for those taking placebo was seen”. However, in the discussion, it was declared that “Those consuming placebo increased in reaction time speed on the same task (stroop test) at V4. It seems there is a contradiction between results and discussion.

Thank you for highlighting this. We have corrected the statement in the discussion to reflect the correct direction of outcome.

- Discuss the generalizability of the finding in the discussion section.

We thank you for this note. We have added some notes on the generalizability of the findings on page 19:

“The current research highlights the potential for families witnessing the negative impact of ADHD symptoms on a family members academic performance, to explore a safe, alternative option to pharmacotherapy. The population of children and adolescents experiencing these symptoms is widespread, making the generalizability of these findings considerably important in this context. The extensive list of associated symptoms that vary in severity, require a safe and successful long-term intervention. The lack of significant improvements in behavioural outcome could highlight the potential for further study into dose-ranging of CDRI 08[®] in a similar population with a more restricted age range and symptom profile.”