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Cognitive-behavioural interventions for attention deficit hyperactivity disorder (ADHD) in adults (Protocol)

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[Intervention Protocol]

Cognitive-behavioural interventions for attention deficit hyperactivity disorder (ADHD) in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy of cognitive-behavioural-based therapy as a treatment for adults with ADHD.

BACKGROUND

Description of the condition

According to the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-IV-TR), attention deficit hyperactivity disorder (ADHD) is a developmental condition characterised by symptoms of inattention, hyperactivity and impulsivity (APA 2000). Using these criteria, ADHD can be divided into three types: combined type, predominantly inattentive type and predominantly hyperactive-impulsive type. The International Classification of Diseases (ICD-10) offers a similar definition for hyperkinetic disorders (WHO 1992). Along with these three main symptomatic clusters, people with ADHD also present with deficits in executive functions, behaviour and emotion regulation, and motivation (Brown 2000; Wender 2001; Davidson 2008; Torrente 2011). There is a high prevalence of comorbid disorders, estimated at 50% to 75% (Kessler 2006), including anxiety, depression and substance abuse (Biederman 1993; Murphy 1996). Epidemiological studies estimate that the prevalence of ADHD is around 5% in childhood (Polanczyk 2007) and approximately 2.5% in adulthood (Simon 2009).

Evidence on gender differences in ADHD is controversial. Some authors suggest that there are no differences between females and males (Biederman 2002; Seidman 2006). Other authors, such as Gershon 2002, argue that there are quantitative and qualitative differences in executive functions.

The work of Still is commonly accredited as the first description of a syndrome in children that included some of the characteristics of ADHD (Still 1902). However, the characterisation of the

disorder in adults is more recent and attributed to Wood's work of 1976 (Adler 2002). Since then, many papers have been published that provide evidence on the diagnostic validity of adult ADHD (Spencer 1998). The validity of the diagnosis in adulthood is supported by clinical correlates, family history, treatment response and experimental studies (Faraone 2000). Additionally, longitudinal studies have demonstrated the persistence of the disorder in a large proportion of adults who were diagnosed with ADHD during childhood (Barkley 1999).

As Brassett-Harknett 2007 points out, there are diagnostic difficulties with adult ADHD - the current diagnostic criteria were originally designed for children, but ADHD in adulthood has particular characteristics that differ from the syndrome in childhood. For example, hyperactivity tends to decrease in adulthood (Achenbach 1998), with some studies showing that 90% of adults with ADHD present predominantly with inattentive symptoms (Millstein 1997).

Importantly, the persistence of ADHD in adulthood has been recognised as a clinical problem with serious health consequences (Wilens 2004; Davidson 2008). Barkley 2008 highlights the severe occupational consequences of the disorder, such as lower occupational status and annual salaries compared to a control group, worse employer-rated job performance, more job dismissals and frequent changes of job. Those who suffer from ADHD are less capable of fulfilling work demands, less likely to be working independently and complete tasks, and less likely to get along well with supervisors as rated by employers. They have poorer performance at job interviews and find certain tasks at work too difficult. Additionally, Stevenson 2002, referencing Woods' studies, suggests that people with ADHD experience anger dysregulation as a highly associated psychosocial problem. ADHD also carries psychological consequences since repeated life experiences of frustration undermine self concept and self esteem, leading to the formation of negative beliefs about the self, which, in turn, affect quality of life and emotional adjustment (Torrente 2012).

Description of the intervention

Since ADHD has been shown to persist in adulthood, diverse psychological treatments have been developed for this population in recent years (Knouse 2008; Weiss 2008). Most of them were inspired by cognitive-behavioural therapy (CBT) and were designed to be implemented as adjunctive interventions to pharmacological treatment (Safren 2006). As is usual in CBT treatments, the interventions are organised into relatively brief and focused, structured protocols. Most CBT programmes for adults with ADHD take between eight and 12 sessions and can be delivered on an individual or group basis. The main objectives of the treatment are to change habitual modes of behaving that reinforce detrimental effects of the disorder by teaching techniques that will allow people with ADHD to control the core symptoms of ADHD, and to improve emotional adjustment, self esteem and common comorbid symptoms such as anxiety and depression. As regards psychotherapeutic techniques, proposed methods include psychoeducation for increasing consciousness and understanding of the disorder. They also involve cognitive techniques for restructuring the dysfunctional thoughts and maladaptive beliefs that reinforce emotional maladjustment. Finally, behavioural interventions and cognitive remediation methods intend to provide new, healthy, compensatory strategies and skills for deficient attention, executive functioning, impulse control and emotion regulation (Ramsay 2010).

Variants of the classical CBT approach have been applied to this population, such as dialectical behavioural therapy (Hesslinger 2002; Philipsen 2007) or meta-cognitive therapy for adults with ADHD (Solanto 2010). Although these variants share the more general principles of CBT as described in the next section, they emphasise different types of interventions such as emotion regulation skills in dialectical behavioural therapy and cognitive training methods in meta-cognitive therapy. Because they share the general model and procedures of CBT, previous, non-systematic reviews usually included these methods within the broad spectrum of CBT interventions (Knouse 2008; Weiss 2008). Yet, these types of CBTs have never been directly compared with each other so it is unknown if they have different treatment effects. Moreover, comparing CBT with placebo, waiting list and no treatment could have different treatment effects for each comparison and we plan to explore these potential differences in our study.

How the intervention might work

The cognitive-behavioural approach provides a useful framework for understanding how negative life experiences may reinforce functional impairment and lead to increased emotional disturbance in adults with ADHD. Because of neurobiological deficits in attention, executive function and inhibitory control, failure and underachievement in different domains of function are common occurrences in people with ADHD as they enter adulthood (Barkley 2006; Biederman 2006). According to the CBT model, such repeated life experiences of frustration undermine self concept and self esteem, leading to the formation of negative beliefs about the self, which, in turn, favour the expression of negative emotions such as depression and anxiety. Negative self beliefs can also lead to the adoption of maladaptive behavioural strategies, including negation, procrastination and extreme avoidance as a means of coping with difficult tasks (Safren 2006; Young 2007; Ramsay 2008). In addition to emotional disturbances, negative expectations about the future, anticipation of failure and reduced self confidence can also affect motivation (Torrente 2011). The proposed mechanisms of change entail the acquisition of compensatory behavioural and cognitive techniques for improving core attentional and executive deficits of ADHD, and the modification of distorted negative beliefs to promote emotional maladjustment (Ramsay 2010). For this purpose, CBT programmes are

usually organised into several modules with specific techniques for target problems. Most treatments begin with a psychoeducational module in which patients are taught about the disorder and introduced to the rationale for the treatment. The organisation module involves the acquisition of different executive techniques such as goal setting, sequencing and prioritising, devising a time schedule, using a calendar or agenda, making 'to do' lists, monitoring progress, and planning breaks and rewards. Patients also learn problem-solving techniques for articulating problems more clearly, generating a list of potential solutions, evaluating them and finally testing the chosen solution. The distraction management module helps patients to recognise their optimal attention span and organise the tasks according to it, and introduces skills for dealing with distractions such as writing them down and going back to the task, using cues or alarms, or modifying environmental factors. The impulsivity management module includes strategies for self monitoring and self control. The self monitoring module implies the detection of cues and situations that act as triggers for impulsive behaviour while self control strategies refer to the use of self instructions, relaxation techniques or other alternative behaviours. The cognitive restructuring module helps patients to become aware of the ideas that reinforce maladaptive behaviours and emotions, and to replace them with more adaptive thoughts. Currently, research on the clinical usefulness of this intervention is still in development. Several pilot studies have demonstrated the feasibility and acceptability of the approach (Knouse 2008), and more recently a series of randomised controlled studies have provided evidence for the efficacy of CBT for adults with ADHD (Stevenson 2002; Safren 2005; Safren 2010; Solanto 2010).

Why it is important to do this review

Between 20% and 50% of people with ADHD do not respond to drug treatment (Wilens 2002). The consequences of ADHD can have an important, negative impact on different areas of a person's life such as poor academic performance, deficits in social and occupational functioning, greater job insecurity and a greater number of legal problems (Barkley 2002; Davids 2004). An effective psychosocial intervention might bring benefits to one or more of these areas for adults with ADHD. To date, no systematic review has examined the effects of CBT in adults with ADHD. The growing number of randomised controlled trials assessing the efficacy of CBT for this population (Knouse 2008) suggest that this review is timely.

OBJECTIVES

To assess the efficacy of cognitive-behavioural-based therapy as a treatment for adults with ADHD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Adults over 18 years old diagnosed with attention deficit hyperactivity disorder (ADHD) or hyperkinetic disorders (HKD) according to established diagnostic criteria, who have medication stability (less than 10% change in dose) in the two months prior to initial evaluation.

Types of interventions

Individual and group treatments of CBT in any of its variants such as standard CBT, dialectical behavioural therapy or meta-cognitive therapy. We will assess CBT as monotherapy and CBT as a part of combined treatment separately. Each of these will be evaluated as follows:

Monotherapy

- **CBT** versus **control** (supportive psychotherapies, placebo interventions, waiting list or no treatment)
- **CBT** versus **usual treatment** (other specific psychotherapies for ADHD)

Combined therapy

- **CBT combined with pharmacotherapy** versus **pharmacotherapy alone**

Any CBT intervention included must fulfil both of the following criteria:

1. Treatment is aimed at: increasing knowledge of the disorder, identification and restructuring of dysfunctional thinking and maladaptive beliefs, and development of emotional and behavioural compensatory strategies for the core deficits.
2. The sequence of treatment modules is clearly defined.

We will not impose any restriction with regard to the format of the treatment (that is its duration, quantity and frequency of sessions).

Types of outcome measures

We will consider psychometrically validated self report measures or those completed by an independent rater or by a relative. Measures will be considered as short (up to six months), medium (six months to 12 months) and long-term (more than 12 months). We will include studies that have assessed at least one primary or secondary outcome.

Primary outcomes

The core symptoms of ADHD (inattention*, hyperactivity* and impulsivity*) will be assessed as a whole. If study authors report these symptoms separately, we will include the data in the analysis. We will assess the core symptoms using validated measures. For example:

Continuous outcomes:

- Current Symptoms Scale (Barkley 1998)
- Conners Adult ADHD Rating Scales-Self Report: Long Version (Conners 1999)
- Conners Adult ADHD Rating Scales-Observer Report (Conners 1999)

We are unaware of any adverse events having been reported, so it is not possible to be specific about these. If there is an adverse effect in the included studies, we will report it in the analysis

Secondary outcomes

We will assess the following variables as secondary outcomes. The listed measures are only mentioned as examples and the list is not exclusive.

Continuous outcomes:

- Psychopathology (depression and anxiety)*
  - Beck Depression Inventory II (Beck 1996)
  - Beck Anxiety Inventory (Beck 1988)
  - Hamilton Depression Scale (Hamilton 1960)
  - Hamilton Anxiety Scale (Hamilton 1959)
  - State-Trait Anxiety Inventory (Speilberger 1989)
- Anger*
  - State-Trait Anger Expression Inventory (Spielberger 1988)
- Self esteem*
  - Rosenberg Self-Esteem Inventory (Rosenberg 1965)
- Quality of life*
  - Adult Attention-Deficit/Hyperactivity Disorder Quality-of-Life Scale (Brod 2005)

Dichotomous outcomes:

- Employment status (for example, working and/or not working and/or full-time and/or part-time, as defined by study authors)
- All-cause treatment discontinuation (proportion of patients randomised that dropped out from the study due to any cause, such as adverse events of medication)

Outcomes to be included in a 'Summary of findings' table are marked with an asterisk. We will prepare these 'Summary of findings' tables using GRADE methodology (Atkins 2004; Guyatt 2011).

Search methods for identification of studies

We will use the following search terms, which include the Cochrane highly sensitive search strategy to identify randomised trials in MEDLINE (Lefebvre 2008). We will not apply date or language restrictions. We will modify the search strategy as necessary for other databases.

1 "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/
2 ADHD.tw.
3 ADDH.tw.
4 ADHS.tw.
5 ("AD/HD" or hkd).tw.
6 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).tw.
7 ((disrupt$ adj3 disorder$) or (disrupt$ adj3 behav$) or (defian$ adj3 disorder$) or (defian$ adj3 behav$)).tw.
8 (impulsiv$ or inattentiv$ or inattention$).tw.
9 hyperkinesis/
10 (hyperkin$ or hyper-kin$).tw.
11 (minimal adj3 brain adj3 (disorder$ or dysfunct$ or damage$)).tw.
12 (hyperactiv$ or hyper-activ$).tw.
13 or/1-12
14 exp behavior therapy/
15 psychotherapy/
16 "Imagery (Psychotherapy)"/
17 Psychotherapy, Rational-Emotive/
18 Feedback, Psychological/
19 exp Biofeedback, Psychology/
20 ((multi systemic or multisystemic) adj2 therap$).tw.
21 mindfulness.tw.
22 ((aversive or aversion or biofeedback$ or feedback$ or desensiti#ation or relaxation or meditat*) adj3 (therap$ or intervention$ or program* or treatment* or approach* or technique*)).tw.
23 ((cognition or cognitive) adj3 (therap$ or remedation or restructur$ or rehabilitat$ or intervention$ or program$ or psychotherap$ or treatment$ or approach$ or technique$)).tw.
24 (behavio?r$ adj3 (modification$ or therap$ or rehabilitat$ or intervention$ or program$ or psychotherap$ or treatment$ or approach$ or remedation or technique$)).tw.
25 cognitive-behavio$.tw.
26 (CBT or DBT).tw.
27 (metacognitive or meta-cognitive).tw.
28 (social skills adj3 train$).tw.
29 or/14-28
30 13 and 29

31 randomized controlled trial.pt.
32 controlled clinical trial.pt.
33 randomi#ed.ab.
34 placebo$.ab.
35 drug therapy.fs.
36 randomly.ab.
37 trial.ab.
38 groups.ab.
39 or/31-38
40 exp animals/ not humans.sh.
41 39 not 40
42 30 and 41

Electronic searches

We will search the following databases for all available years. Date and language limits will not be applied.

- Cochrane Central Register of Controlled Studies (CENTRAL), part of *The Cochrane Library*
- Ovid MEDLINE
- EMBASE
- LILACS (Latin American and Caribbean Health Sciences Literature)
- CINAHL (Comprehensive Index of Nursing and Allied Health Literature)
- PsycINFO
- BIOSIS Previews
- Cochrane Database of Systematic Reviews,
- Database of Abstracts of Reviews of Effects (DARE)
- ClinicalTrials.gov clinicaltrials.gov
- International Clinical Trials Registry Portal (ICTRP) apps.who.int/trialsearch/
- *meta*Register of Controlled trials (mRCT) controlled-trials.com/mrct/

Additionally, we will search dissertations and abstracts from the following.

- Association for Behavioural and Cognitive Therapies (ABCT) Convention
- World Congress on ADHD, organised by the World Federation of ADHD
- Annual Meeting - American Psychiatric Association (APA)

Finally, we will search for dissertations and theses in open access repositories such as the Networked Digital Library of Theses and Dissertations (NDLTD) ndltd.org/.

Searching other resources

We will consult experts and researchers in the field, including investigators from all review articles and primary studies identified through searches, about ongoing or unpublished trials.

Data collection and analysis

Selection of studies

Two authors (PL, FT) will independently screen titles and abstracts using the Early Review Organizing Software (EROS) (Glujovsky 2010; Ciapponi 2011; Ciapponi 2011a). If it is clear from the title and abstract that the study does not meet the eligibility criteria, it will be rejected. If it is not clear, then we will obtain full text of the study and both review authors will independently evaluate the paper using EROS to determine if the study should be included or excluded. If there is a disagreement, the review authors will try to solve it by reaching a consensus. In the case that consensus cannot be reached, a third author (AC) will independently assess the study and resolve the disagreement.

Data extraction and management

Two review authors (PL, FT) will independently extract data from each of the included studies and enter the information into a proforma designed and piloted for this purpose. We will extract information about 'Risk of bias' criteria and methods of participant selection. We will also extract information about population, interventions, comparisons, outcomes, outcome data, study designs, gender, comorbidity, severity, baseline symptoms and 'Risk of bias' items described in the following section. The authors will resolve any difference of opinion by consensus. If they are unable to do so, a third review author will be included in the decision process. All three review authors will discuss the issue and make a final decision.

Assessment of risk of bias in included studies

We will independently evaluate the risk of bias using EROS. It follows the six criteria described in Table 8.5.d 'Criteria for judging risk of bias in the 'Risk of bias' assessment tool' of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Random sequence generation

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Criteria for a judgement of low risk of bias: the investigators describe a random component in the sequence generation process such as referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots and minimisation.
Criteria for a judgement of high risk of bias: the investigators describe a non-random component in the sequence generation process. Usually the description would involve some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;

- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious, for example: allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests and allocation by availability of the intervention.
Criteria for a judgement of unclear risk of bias: insufficient information about the sequence generation process to permit a judgement of low risk or high risk.

Allocation concealment

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Criteria for a judgement of low risk of bias: participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
Criteria for a judgement of high risk of bias: participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias such as allocation based on:
- an open random allocation schedule (for example, a list of random numbers);
- assignment of envelopes without appropriate safeguards (for example, if envelopes were unsealed or nonopaque or not sequentially numbered);
- alternation or rotation;
- date of birth;
- case record number;
- any other explicitly unconcealed procedure.

Criteria for a judgement of unclear risk of bias: insufficient information to permit a judgement of low or high risk. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement; for example, if the use of assignment envelopes is described but it is unclear whether envelopes were sequentially numbered, opaque and sealed.

Blinding of participants and personnel

Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Criteria for a judgement of low risk of bias may involve any one of the following:
- no blinding or incomplete blinding, but the review authors judge that the results are unlikely to be influenced by lack of blinding;
- blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.

Criteria for a judgement of high risk of bias may involve any one of the following:
- no blinding or incomplete blinding, and the results are likely to be influenced by lack of blinding;
- blinding of key study participants and personnel attempted, but it is likely that the blinding could have been broken, and the results are likely to be influenced by lack of blinding.

Criteria for a judgement of unclear risk of bias may involve any one of the following:
- insufficient information to permit a judgement of low risk or high risk;
- the study did not address this outcome.

Blinding of outcome assessment

Detection bias due to knowledge of the allocated interventions by outcome assessors.
Criteria for a judgement of low risk of bias may involve any one of the following:
- no blinding of outcome and/or outcome assessment, but the review authors judge that the outcome and its measurement are unlikely to be influenced by lack of blinding;
- blinding of outcome and outcome assessment ensured, and it is unlikely that the blinding could have been broken.

Criteria for a judgement of high risk of bias may involve any one of the following:
- no blinding of outcome and/or outcome assessment, and the outcome and its measurement are likely to be influenced by lack of blinding;
- blinding of outcome and/or assessment, but it is likely that the blinding could have been broken, and the outcome and its measurement are likely to be influenced by lack of blinding.

Criteria for a judgement of unclear risk of bias may involve any one of the following:
- insufficient information to permit a judgement of low risk or high risk;
- the study did not address this outcome.

Incomplete outcome data

Attrition bias due to the amount, nature or handling of incomplete outcome data.
Criteria for a judgement of low risk of bias may involve any one of the following:
- no missing outcome data;

- reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate;
- for continuous outcome data, the plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on the observed effect size;
- missing data have been imputed using appropriate methods.

Criteria for a judgement of high risk of bias may involve any one of the following:
- the reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate;
- for continuous outcome data, the plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce clinically relevant bias in the observed effect size;
- 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
- potentially inappropriate application of simple imputation.

Criteria for a judgement of unclear risk of bias may involve any one of the following:
- insufficient reporting of attrition or exclusions (or both) to permit a judgement of low risk or high risk (for example, number randomised not stated, no reasons for missing data provided);
- the study did not address this outcome.

Selective reporting

Reporting bias due to selective outcome reporting.
Criteria for a judgement of low risk of bias may involve any of the following:
- the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for a judgement of high risk of bias may involve any one of the following:
- not all of the study's pre-specified primary outcomes have been reported;
- one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (for example, subscales) that were not pre-specified;
- one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for a judgement of unclear risk of bias: insufficient information to permit a judgement of low risk or high risk. It is likely that the majority of studies will fall into this category.

Other bias

Criteria for a judgement of low risk of bias: the study appears to be free of other sources of bias.
Criteria for a judgement of high risk of bias: at least one important risk of bias exists. For example, the study:
- had a potential source of bias related to the specific study design used; or
- has been accused of bring fraudulent; or
- had some other problem.

Criteria for a judgement of unclear risk of bias: there is a risk of bias, but there is either:
- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

Measures of treatment effect

Continuous data

We will calculate mean differences (when studies use the same measure) or standardised mean differences (SMDs) (when studies use different measurement scales) and 95% confidence intervals (CIs) for continuous outcome measures. When necessary, we will calculate effect estimates from P values, t statistics or other available statistics.
For those studies which provide only change scores, we will perform separate analyses to those studies which provide only final values. We will combine both values using the generic inverse variance method (Higgins 2011).

Dichotomous data

Where dichotomous data are presented, we will calculate the risk ratio (RR) with a 95% CI as most readers find it easier to understand than the odds ratio (OR) and risk difference (RD).

Unit of analysis issues

For each included study, we will determine the appropriateness of the unit of the analysis for unit of randomisation and the design of each study (the number of observations must match the number of units that were randomised). We expect to find trials with a simple parallel-group design, with participants randomly allocated as individuals, and a single measurement collected and analysed for each outcome from each participant. If we find eligible trials in which i) there are multiple treatment arms, ii) individuals underwent more than one intervention (cross-over trials), or iii) groups of individuals were randomised together (cluster-randomised trials), we will follow the guidance on statistical methods for the type of trial in question as provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and described below.

Cross-over trials

As the length of any effect of CBT is unknown, to avoid a possible carry-over effect we will only use first-period data from any cross-over trials that fit the inclusion criteria.

Trials with multiple treatment groups

In the first instance we will combine results across all eligible treatment arms and compare them with the combined results across all eligible control arms, making single, pair-wise comparisons. Where such a strategy prevents investigation of potential sources of heterogeneity, we will analyse each treatment arm separately (against a common control group), but divide the sample size for common comparator groups proportionately across each comparison (Higgins 2011, section 16.5.4). This approach prevents inappropriate double-counting of individuals.

Cluster-randomised trials

We do not anticipate finding cluster-randomised trials because this design is uncommon in this field. If investigators report cluster-randomised trial data as if the randomisation was performed on the individuals rather than the clusters, we will request individual participant data to calculate an estimate of the intracluster correlation coefficient (ICC).

If individual participant data are not available, we will obtain external estimates of the ICC from similar studies or available resources (Campbell 2000). Once established, we will use the ICC to re-analyse the trial data to obtain approximate, correct analyses as described in Section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We plan to combine the effect estimates and their corrected standard errors from cluster-randomised trials with those from parallel-group designs using the generic inverse variance method (Higgins 2011). If the available information is not enough to control for clustering in this way, we will enter the data into the Review Manager 5 software (RevMan 5) using individuals as the unit of analysis (Review Manager 2012). We will then perform sensitivity analyses to assess the potential bias that may have occurred as a result of the inadequately controlled clustered trials. Also, if the ICCs were obtained from external sources, we will perform sensitivity analyses to assess the potential biasing effects of inadequately controlled cluster-randomised trials (Donner 2001).

Dealing with missing data

Where necessary, we will contact the corresponding authors of included studies, up to three times, to supply any unreported data. If studies have not reported the standard deviation (SD), we will calculate it from P values, t values, CIs or standard errors (as described in section 7.7.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011). If this information is not reported, or is unattainable, we will impute the SD from the study with the highest SD for that outcome. To assess the effect of this assumption on the analysis, we will conduct a sensitivity analysis for that outcome by comparing the results of analyses with our imputed 'highest SD' versus analyses that use a SD imputed from the study with the lowest SD.

If outcome data are reported as a median or range, or as a mean without a variance, we will report the data in additional tables.

We will describe missing data and drop-outs for each included study in the 'Risk of bias' table, reporting reasons, number and characteristics of drop-outs, and we will discuss the extent to which the missing data could alter our results. We will conduct sensitivity analyses to assess the effect of missing dichotomous data on our primary meta-analyses by assuming, on the one hand, that all missing data were successes, and on the other hand that all missing data were failures (best versus worst-case scenario analyses).

We will make no assumptions about loss to follow-up for continuous data, and we will base analyses on those participants completing the trial.

Assessment of heterogeneity

We will appraise the extent of clinical heterogeneity among the studies by comparing the distribution of participants characteristics (comorbidity, severity, baseline symptoms, ADHD subtype), study factors (randomisation, allocation concealment, blinding of outcome assessment, losses to follow-up, treatment type, type of control group, co-interventions, different types of outcome measurements). We will assess these variables by subgroup analysis if

I^2 is more than 30%. Also, a low P value for the Chi^2 test (< 0.1) will be deemed sufficient reason to explore causes of heterogeneity. We will describe statistical heterogeneity of intervention effects by calculating the I^2statistic and using the Chi^2 test. Thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors. We will interpret it as follows:

- 0% to 30%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- more than 60%: may represent substantial or considerable heterogeneity.

Assessment of reporting biases

In the case that at least 10 studies can be included, we will use funnel plots to detect bias. Funnel plot asymmetry could be due to publication bias, but it could also be due to a real relationship between trial size and effect size such as when larger trials have lower compliance and compliance is positively related to effect size. In general, asymmetry may be due to selection biases (publication bias, delayed publication bias, location biases, selective outcome reporting), poor methodological quality leading to spuriously inflated effects in smaller studies (poor methodological design, inadequate analysis, fraud), true heterogeneity or chance (Egger 1997). We will use the test proposed by Egger 1997 for continuous outcomes to test for funnel plot asymmetry (Higgins 2011).

Data synthesis

Where we consider studies to be sufficiently homogenous in terms of participants, interventions and outcomes, we will synthesise the results in a meta-analysis using RevMan (Review Manager 2012). We will use both the fixed-effect model and the random-effects model and compare them in order to assess the degree of statistical heterogeneity. Because we assume that clinical heterogeneity is very likely to impact on our review results given the nature of the interventions included, we will primarily report the random-effects model results, regardless of statistical evidence for heterogeneity. We will calculate all effects using inverse variance methods. For continuous data, the change in score from baseline to post-intervention is the main outcome of interest. For continuous data reported as change scores in some studies and final values in other studies, we will analyse these data separately. Also we will combine these values using the generic inverse variance method (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

If it is possible to secure the necessary data, we will conduct subgroup analyses classifying the trials as follows.

1. Type of ADHD subtype: inattentive, hyperactive-impulsive or combined type.
2. Type of CBT: standard, dialectical behavioural therapy or meta-cognitive therapy.
3. Type of control group: placebo, waiting list or no treatment.

We will calculate a pooled effect size for each subgroup.

Sensitivity analysis

We will use sensitivity analyses to assess the impact of risk of bias on the results of the primary analyses. For this review, we will undertake sensitivity analyses to determine the effect of restricting the analysis to: (a) only studies with low risk of selection bias (associated with sequence generation or allocation concealment), (b) only studies with low risk of performance bias (associated with issues of blinding), and (c) only studies with low risk of attrition bias (associated with completeness of data). In addition, we will assess the sensitivity of findings to any imputed data within a study. We will investigate the impact of applying a fixed-effect model on the results compared to a random-effects model. We will also compare the impact of using OR as an effect measure compared to RD.

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

All authors participated in drafting the protocol. Pablo López, Fernando Torrente and Agustín Ciapponi prepared the search strategy.

DECLARATIONS OF INTEREST

Pablo Luis Lopez - none known.

Agustín Ciapponi - none known.

Marcelo Cetkovich-Bakmas - none known.

Juan Ignacio Rojas - none known.

Alicia Graciela Lischinsky - received payment as an invited speaker, at Ely Lilly and Jannsen Labs.

Fernando Manuel Torrente - none known.

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