Third generation cognitive behavioural therapy versus treatment-as-usual for attention deficit and hyperactivity disorder: a randomized, 2-parallel-group, evaluator blinded, superiority trial

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Study protocol

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Abstract

Background

This study aims to compare improvements in Attention Deficit and Hyperactivity Disorder (ADHD) symptom severity between a group of ADHD children and parents undergoing a new therapeutic program based on third generation cognitive-behavioural therapy (Hyper-mCBT) and a similar group undergoing treatment-as-usual with the Barkley program.

Methods

248 children diagnosed with ADHD will be randomly assigned to either a Hyper-mCBT program or a Barkley program. This is a randomized (1:1), 2 parallel-group, superiority trial with evaluator blinding and stratification according to center and methylphenidate treatment. Hyper-mCBT program consists in a series of 16 simultaneous-but-separate therapies sessions for parents and for children.

Discussion

More effective psychotherapeutic approaches are needed for ADHD children. Pharmacotherapy seems to be more effective in reducing ADHD symptoms but it is not always helpful, carries side effects and it is rejected by many parents/professionals. Results for psychotherapy programs for ADHD are inconsistent although several studies have shown clinical improvements. This trial will substantiate encouraging preliminary results of an innovative psychotherapy program for both parents and children.

Trial registration:

Sponsor Number: PHRC-N/2016/JLC-01

RCB Identification: 2017-A01349-44

Clinicaltrials.gov registration: NCT03437772 (first posted: February 19, 2018)

Introduction

Background and rationale:

Attention Deficit and Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by abnormally elevated levels of inattention, impulsivity and hyperactivity that cause functional impairment in the personal and socio-professional domains. According to a review gathering information from 103 studies across the globe, ADHD, as defined by the International Classification of Diseases (ICD-10), is present in about 5.3% of school-aged children (Polanczyk et al., 2007). Another review by the same group confirmed the stability of ADHD prevalence rates over the last 30 years (Polanczyk et al., 2014). It is interesting to note that ADHD represents 1/3 of consultations in child / adolescent psychiatric settings (Tarver, Daley & Sayal 2014). Apart from the behavioural and attentional problems that it causes, children

and adolescents with ADHD have been qualified as socially disadvantaged, reporting low self-esteem and deficits in emotional and behavioural regulation (Anastopoulos et al., 2011). In their adulthood, ADHD children present an increased risk of educational failure, unemployment, mental disorders, car accidents, substance abuse, interpersonal problems, and law-breaking behaviours (Biederman et al., 2009; Breyer, Lee, Winters, August, & Realmuto, 2014; Charach, Yeung, Climans, & Lillie, 2011; Klein et al., 2012).

Concerning the ADHD treatment, international and French guidelines advocate a multidimensional approach. The psychosocial approach is used in the first intention. When ADHD symptomatology persists or worsens, the medical treatment (methylphenidate) can be used in second intention. Most research has focused on drug treatments since the latter have shown higher efficacy in decreasing ADHD symptoms.

Treatment recommendations are based on a rich but very heterogeneous corpus of literature (Taylor et al. 2004; MTA Cooperative Group 2004; Kendall et al. 2008; Haute Autorité de Santé 2015). The association of methylphenidate and CBT seems to be superior to pharmacological treatment alone, favoring a reduction of ADHD symptoms and an improvement in global functioning (Jensen et al. 2001b; Purdie et al. 2002; MTA Cooperative Group 2004; Majewicz-Hefley & Carlson 2007). Indeed, the ADHD Observational Research in Europe (ADORE) study has shown that the most significant short-term effects were obtained using medications but over the long-term a combination with psychotherapy was more efficient (Falissard et al. 2010). However, there is a strong heterogeneity among studies, including different measures and raters, and varying endpoints, that precludes the drawing of any firm conclusion (Hodgson et al. 2014) and stresses the importance of assessor-blinding for future studies (Sonuga-Barke et al. 2013).

In practice, the most widely used and studied psychosocial intervention is the parental training programs (Hauth-Charlier and Clément, 2009). Literature shows that such programs have a positive influence on parental well-being, parental ability to cope with child behavior problems, parent-child relationships, and child behaviors (Anastopoulos et al., 1993; Barkley et al., 2000, Barkley et al., 2001, Sonuga-Barke et al., 2001).

Several reasons justify the interest of an integrated psychotherapy program that goes beyond parental guidance to improve ADHD symptoms in the long term. On the one hand, metanalytic reviews have only found partial support for nonpharmacological interventions for ADHD, either applied to parents or children, and they highlight the need of more research into psychological treatments (Hodgson et al. 2014, Storebo et al., 2019). Previous studies have demonstrated the superiority of simultaneous care for both parents and children versus children or parents alone (Horn et al. 1990; Kim & Yoo 2013). On the other hand, the effectiveness of pharmacotherapy is often reduced, especially in the presence of comorbidities (80% of children with ADHD) and a growing number of parents / professionals are reluctant to try drug treatments. If they do try them, the effects of drug therapy diminish over time. Our preliminary data in a pilot non-controlled small sample (n = 30 unpublished) suggests that the use of last-generation CBT practices, such as mindfulness (Mah et al., 2020), in an integrated program for parents and children may be more effective than parental guidance alone. We have termed this program Hyper-

mCBT, a unique combination of parental guidance with psychotherapeutic interventions for ADHD children and their parents.

Objectives:

According to preliminary clinical data, we hypothesize that the Hyper-mCBT program will reduce the symptoms of ADHD and anxiety / depression scores, while improving the levels of self-esteem, emotional control, social integration and academic achievement. The primary objective of this study is to compare improvements in ADHD symptom severity between a group of ADHD children and parents undergoing the Hyper-mCBT program and a similar group undergoing treatment-as-usual with the Barkley program. The evaluation of ADHD severity will be made at 5 and 8 months post-inclusion. The secondary objectives of this study are to compare the randomized groups concerning: parenting styles and parental quality of life, anxiety and depression levels in both children and parents, and social well-being, school parameters, self-esteem, global functioning, and behaviour in participating children.

Trial design:

This is a randomized (1:1), two parallel-groups, superiority trial with evaluator blinding and stratification according to centre and methylphenidate treatment.

Methods

Study setting:

The trial takes place in several public psychiatric hospitals in France and is coordinated by Nimes University Hospital. The clinical aspects of this trial take place within participating academic/public hospitals (urban setting) located in France: Nimes, Montpellier and Paris.

Eligibility criteria:

Participants are children between 7 and 15 years of age presenting an Attention Deficit and Hyperactivity Disorder (ADHD Rating Scale Parent Version: Investigator Administered and Scored ADHDRS-PI> 27). The patient and the parents (or legal guardians) give their informed consent and are insured or beneficiaries of a health insurance plan. Regarding treatment, the patient may either be treated with a stable dosage of methylphenidate (not expected to vary in the near future) and remain symptomatic, or not be on treatment.

Participation in another trial or study that may interfere with the results or conclusions of this study is a criterion of exclusion. Similarly, if the patient is in a period of exclusion determined by a previous study. Participants whose parent (s) is (are) under judicial protection or is an adult under guardianship, are also excluded from the study. In addition, the family cannot be included if it is impossible to properly inform the patient, his / her parents or legal guardian, and if the patient or parents refuse participation, signature of signed consent or follow-up procedures. If the investigator suspects of or if there is documented information about an intellectual disability (IQ <70), the patient is excluded. The same applies to patients

diagnosed with autism spectrum disorder, psychotic disorder or bipolar disorder. Finally, the patient should not be involved in cognitive-behavioral therapy (individual or group) during the six months prior to inclusion and / or have previously participated in this study. Written informed consent is obtained from all participants by the investigators (senior psychiatrists or psychologists) after explaining the purpose and methodology of the study (please see Declarations/Ethics for more details).

Interventions:

Interventions take place during the school year to avoid perceived seasonal differences in children's stress levels (among others). Participation in the study is systematically proposed to all ADHD children/adolescents and their parents meeting eligibility criteria. We selected the Barkley program as a comparator since it is the most used and studied parental training program and there is consistent evidence on its benefits (see introduction). The study is presented to patients and their parents as a clinical trial to compare treatments with similar benefits, along with appropriate information letters. If the patients/parents show interest in the study, the first evaluation visit is organized.

At the end of the first evaluation visit, randomization occurs to assign the patient either to the experimental group (mCBT) or the comparator group (treatment as usual (TAU): Barkley therapy). At this time, only a designated person in charge of organizing therapy sessions is aware of the randomization results.

Experimental group (mCBT)

The mCBT program is a 3rd generation cognitive behavioural therapy program that combines social skills training, emotional regulation, self-esteem, cognitive remediation and mindfulness therapies for children and behavioural techniques, emotional regulation and mindfulness for parents. This program consists in a series of 16 simultaneous-but-separate therapies sessions for parents and for children (see Supplementary Table 1 for details). Each of the 2×16 sessions will last 75 minutes every week. To facilitate the participation of children the duration of the sessions was reduced to 75 minutes, but the total amount of therapy during the program is similar to the comparator group. Parents participate in the parental guidance program with their therapist (psychologist or psychiatrist), and children participate in their own program with their own therapists (1 leader and 1-2 regulators). The simultaneous nature of the program avoids excessive impact on the daily life of families. The therapists are trained in cognitive behavioural therapy.

Children group: The first therapist, or "leader" runs the session and is considered as the teacher or "facilitator", the second therapist, the "regulator", manages the behaviour of the children and the group and the organizational aspects. When many children are present, it may be appropriate for three adults to be present, with a second adult regulating "disruptive" behaviour and accompanying some children back to calmness while the first regulator concentrates on reinforcement activities.

Children's groups are formed according to age and school level in order to encourage a sentiment of "belonging". The vocabulary and techniques used are adapted to each group's age level and cognitive abilities. The place where children's sessions take place is important. The room must be simple with few distractors. Seating should be arranged in a U shape to facilitate interaction. Seating should also be quiet in nature (e.g. put tennis balls on chair legs to avoid scraping noises). The session leader is positioned in front of the children next to a paperboard or a slideshow. The regulator freely moves around the room as required or preferentially stays near the back. Seating arrangements for children should be discussed before sessions in order to avoid unwanted interactions. During such sessions with ADHD children, the participating therapists must allow for a certain amount of acceptable agitation and define strategies that help children self-regulate their behaviour.

The therapists are encouraged to use a timer. The first 60 minutes are dedicated to the session, and the last 15 to a summary and review of material covered during the session in order to help emphasize the overall take-home message, to the children's mission to be performed at home or school, to self-evaluation and finally an end-of-session game. A bell can be used to signal the beginning and end of each activity, mediation time, etc.

All sessions present the same structure: the group starts with a reminder about the rules, after the mediation "today's weather and stress thermometer", then a review of the previous session's missions. Then comes the sequence of the day which must have a visual support (slides, or posters) describing the content of the session. The session ends with a session summary, the new missions and the child makes a self-evaluation of his behavior. To conclude there is an End-of-session game.

Parent session: This program is largely inspired by the Russel Barkley program into which have been integrated other tools like mindfulness, acceptance and commitment therapies (ACT) and nonviolent resistance. We adapted these therapeutic techniques in our clinical practice and recommend that they be coupled with a support group for children with ADHD.

The aim of the integrative therapeutic parent group is to offer 16 sessions of integrative therapy on the various spheres of life of the child affected by ADD / ADHD to promote a better quality of life and well-being for the child and family. The parent is placed in a co-therapist position, pledging to initiate change in his/her relationship with his/her child. He/she should not expect an immediate positive reaction from the child. The parent has the responsibility of avoiding any manifestation of verbal or physical violence. Sessions with parents are led by a single therapist trained in cognitive behavioural therapy. Therapists are encouraged to use a visual time cue, such as a timer. The timer can give an indication of the time remaining in the session. For a 75 minute session, the first 30 minutes are devoted to a review of the tasks performed and the last 45 minutes are devoted to the meeting and presentation of new missions. The place where parental sessions take place is important. The layout of the environment is essential to ensure optimal attentional mobilization, to promote exchanges not only between therapist and parents but also among parents. The room is uncluttered with few distractors, the seats are installed in a U to

promote interaction. The therapist is positioned in front of the parents before the Paperboard or Powerpoint. The structure of a typical session is described in Table 1.

Control group (Barkley program)

The Barkley program is specifically conceived for parents of children with ADHD, either individually or in groups of 6 to 8 families, with twelve 90-minute sessions, occurring twice a month. The objective of this program is to train parents to cope with the difficult situations they encounter, to learn effective control strategies that are coherent and adapted to the 'deviant' behaviour of their children in order to reduce the intensity of events and their consequences on family life. All this inevitably involves improvement of family relationships through an essential improvement of the image that parents have of themselves, the image the child has of him/herself and overall family functioning.

Each session focuses on a "theme" or a particular situation: practical exercises are offered to families to improve communication, adjust the educational responses, analyse the behaviour of the child and anticipate crises in order to avoid them. These practical exercises are practiced at home. A typical session has the following structure: 30 min review of exercises practiced at home, 60 min: theme of the day's and new exercises.

Control group facilitator cannot participate in mCBT therapy to avoid bias. The Barkley program is already in use by all participating centers and training per se is not required. Nevertheless, a standardized consensus has been established between the centers to reduce variability before beginning the study and regular meetings are made annually to ensure that the program is followed faithfully.

Outcomes and data collection:

Three evaluation times are realized (inclusion, after 5 months and after 8 months). During the evaluation carried out by a blinded evaluator, questionnaires and self-questionnaires are carried out:

The first objective of this research is evaluated by the ADHDRS-PI questionnaire in an interview with the parent(s) and the patient. The 18 items correspond to the 18 symptoms listed in the DSM-IV ADHD diagnosis. The reliability and validity of the ADHDRS-PI has been studied in a panel of European countries, including France (Zhang et al. 2005; Döpfner et al. 2006).

Several secondary outcomes are evaluated:

- A: **The parental authority questionnaire** (PAQ) auto questionnaire to compare changes in parenting styles between groups. It consists of 30 items per parent and yields permissive, authoritarian, and authoritative scores for both the mother and father (Buri 1991).

- B: **Parental – Developmental Disorders – Quality of Life** (PAR-DD-Qol). To compare changes in the quality of life for parents between groups. This auto-questionnaire contains 17 items. (Raysse 2011)

- C: To compare changes in global function between groups:

The Children's Global Assessment Scale (CGAS): The CGAS was designed by Shaffer et al. (1983) based on the Global Assessment Scale (Endicott et al. 1976) and was subsequently found to have discriminant and concurrent validity (Bird et al. 1987). It is widely used today as a clinician-rated scale assessing the overall functioning of a child based on all available information (Lundh et al. 2010).

The Clinical Global Impressions Scale (CGI-S): Is a seven-point scale used by an investigator to rank the severity of illness observed for a given patient. The CGI-S was developed for use in clinical trials to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating a study treatment.

- D: To compare changes in social well-being and school parameters for children between groups:
CONNERS 3rd Edition for school teachers. The evaluation of the child's behaviour is performed using the Conners questionnaire for teachers (Conners 2008).

- E: To compare changes in anxiety and depression (for both children and parents) between groups.
Multidimensional anxiety scale forchildren in 10 items (MASC-10): The MASC items approximate the DSM-IV anxiety diagnoses and contains four factors: a physical symptoms (tense/somatic), a harm avoidance (perfectionism/anxious coping), a social anxiety (humiliation/performance fears), and a separation anxiety / panic. The full MASC has shown good internal consistence and test-retest reliability. (March et al. 1997, 1999; March & Sullivan 1999; Rynn et al. 2006; Baldwin & Dadds 2007)

Children depression inventory2 (CDI2-short version): An evaluation of a depressive episode is performed using the Children's Depression Inventory, a hetero-questionnaire developed by Bae (2012). This is a 12 item questionnaire which assesses depression in children of 7 to 17 years of age.

Hospital anxiety and depression scale (HADS): Auto questionnaire for adult, developed by Zigmond & Snaith (1983); Snaith & Zigmond (1986); Herrmann (1997); Bjelland *et al.* (2002); Snaith (2003), which is validated in French (Lépine *et al.* 1985; Untas *et al.* 2009), is commonly used to screen for anxiety and depressive disorders in clinical studies. The HADS questionnaire has 14 questions, including 7 questions concerning anxiety and 7 concerning depression.

- F**:** To compare changes in self-esteem and behaviour for children.

Rosenberg Scale: The auto questionnaire is for children, which measures global self-esteem and is composed of 10 items for which the subject must give his/her level of agreement. (Rosenberg 1965)

CONNERS 3rd Edition for parents: The evaluation of the child's behaviour is performed using the Conners auto questionnaire for parents. This is a behavioural observation questionnaire for children from 6 to 18 years of age. (Keith Conners 2008).

And to finish, two diagnostic questionnaires:

The Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL) are used. This is a semi-structured diagnostic interview that assesses current and past episodes of psychopathology in children and adolescents according to DSM-III-R and DSM-IV criteria. Published study results indicate that the K-SADS-PL generates reliable and valid child psychiatric diagnoses (Kaufman et al. 1997).

Adult ADHD self-report scale (ASRS): was designed by researchers from the New York University and Harvard medical schools in collaboration with the World Health Organization (WHO). The ASRS is an auto-questionnaire composed of eighteen questions which reflect DSM-IV criteria and address current ADHD symptoms in adults (Kessler et al. 2005; Adler et al. 2006).

Participant timeline:

The study is presented to children and their parents during a selection visit, along with appropriate information letters. If the children/parents show interest in the study, the 1st evaluation visit for the parents and children is organized and their group assignment occurs. Therapy begins after randomization and lasts about 5 months. Then evaluation visits at 5 months (after therapy) and 8 months (post-therapy evolution) are planned. The timeline of the therapy is summarized in Figure 1 and Figure 2.

Sample size:

We could not find prior studies on psychological interventions for ADHD using a similar sample, assessments, and research outcomes. Thus, to estimate the sample size we used: i) preliminary data collected from a pilot study on the experimental intervention (n = 30, personal data), and ii) previous data on the efficacy of the Barkley program on a large sample (van den Hoofdakker et al., 2007). We compared the change in the number of patients fulfilling the diagnostic criteria for ADHD in both samples from baseline to the end of the therapy, although the assessment instruments were different (ADHD-Rating Scale in our sample versus the Conners Parents Rating Scale).

To highlight a difference of relative reduction of risk of 9% (SD = 20.6%) between the two groups: 15% parental guidance (van den Hoofdakker *et al.* 2007) versus 24% mCBT (Gramond, personal data), with a two-sided alpha risk of 5% and a power of 90%, it is necessary to recruit 111 children per group. To take account of a potential 10% loss during follow-up, 124 children per group will be recruited, i.e. 248 children. The statistical unit corresponds to a family, which includes a calculated sample size of children with ADHD plus one or both parents.

Recruitment:

Approximately 650 families per year consult at Nimes University Hospital requesting help in dealing with an ADHD child. As this is the smallest establishment participating in this protocol, we expect larger potential recruitment pools for the other centres. Our target rhythm for inclusions is 1-2 families per month and per centre (on average).

This is largely inferior to potential recruitment pools in order to take into account the time constraints associated with randomized group therapy, the need to implement the interventions during the school year, the possibility that certain families may choose not to participate and also to have a feasible inclusion curve.

Assignment of interventions:

Allocation:

Families are randomized to either study arm in a 1:1 ratio. Randomization lists consisting of centralized randomly-sized blocks are established per centre. These lists are the responsibility of an independent methodologist at the BESPIM. A specifically designed SAS program (Cary, NC, USA) is used to carry out randomization.

Patient inclusions are performed via an online software called « Inclusio » (inclusio.bespim.fr), an inclusion-randomization software designed for clinical research projects. Following user login, patient identification (first letter of last name + first letter of first name + year of birth) and verification of screening and exclusion criteria, the treatment number for blind studies or the study arm for open-label studies are indicated to the user. It is impossible to modify the order of randomization; patient assignment to a study arm and a randomization number is definitive. The program provides real-time inclusion alerts to study staff requesting such alerts.

The allocation sequence is generated by an independent methodologist at the BESPIM. Patient enrolment is carried out by including psychiatrists. Randomization is carried out after patient inclusion and after baseline assessments by participating psychologists (i.e. not the including psychiatrists, who are also the outcome-assessors). The e-santé team at the BESPIM is in charge of setting up Inclusio for the needs of the project (note: statistical analyses are carried out at the family level and safety reporting is carried out at the individual level).

Blinding:

Baseline assessments are made before randomization, so these are blinded.

Due to the nature of the intervention neither participants nor staff can be blinded to allocation, but are strongly inculcated not to disclose the allocation status of the participant at the follow-up assessments. Patients cannot be blinded, but are asked to not reveal their group status to anybody outside their group, not even their treating psychiatrist. Furthermore, the hypotheses tested are not communicated to patients (i.e. the patient are not informed on the supposed superiority of one group over another). Therapy care providers (psychologists) cannot be blinded. In order to make assessments as objective as possible, outcome assessors (psychiatrists) are different from the therapy providers (psychologists), and every attempt is made to keep outcome assessors blinded to patient group status. To control for the success of blinding, a “guess-the-group” question is addressed to outcome assessors. Outcome assessor responses are compared to expected results due to chance (see the statistical analyses section).

Data analysts will not be involved in trial field logistics and will be blinded. During analyses, when group assignments are first required they will only be revealed as “group A” or “group B”. Only when analyses have been completed will the exact nature of groups be revealed.

Data collection and management:

Data collection:

Clinical observations are recorded in the case report form as the study progresses.

The instruments / questionnaires to be administered:

1. Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL)
2. The Clinical Global Impression Scale (CGI-S)
3. The Children’s Global Assessment Scale (CGAS)
4. ADHDRS-PI
5. Children’s Depression Inventory (Kovacs 1981)
6. Adult ADHD Self-Report Scale (ASRS)
7. the Parental Authority Questionnaire (PAQ)
8. Parental – Developmental Disorders – Quality of Life (PAR-DD-Qol)
9. Hospital Anxiety and Depression Scale (HADS)
10. The Conners questionnaire for parents
11. Multidimensional Anxiety Scale for Children (MASC)
12. Rosenberg Self-Esteem Scale
13. The Conners questionnaire for teachers

The study clinical research technician maintains contact with families and teachers. Study calendars are distributed to families as early as possible in the study, and kept up-to-date by the study clinical research technician. Reminders are sent to families in the week preceding each evaluation.

Data management: Performed in line with the international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). The related documents is stored on the Department of biostatistics, epidemiology, public health and medical information at the Nimes University Hospital (BESPIM). Electronic Case Report Form (eCRF) fields are formatted so as to enforce homogenous value types and require confirmation especially for out-of-expected-range values. All modifications are fully traceable (who, when, why?) to allow a complete audit trail. An electronic signature by the investigator engages his/her responsibility. The software used to create eCRFs is hosted on a website within Nimes University Hospital. Access to this software is secured via a password. The data collected through generated eCRFs are subject to daily backup on a secure network. The network is

connected to the Internet; access is protected by a firewall. Clinical study data is stored in a specific directory on the server. Only network administrators and BESPIM authorized professionals have access to this directory.

Data management and statistical analysis is provided by the BESPIM. The conditions of transfer of all or part of the research database are decided by the research sponsor and are subject to a written contract.

The following measures are taken to implement confidentiality:

- The required information technology is located at the BESPIM; access is controlled and secured.
- Data are stored on a server hosted in a secure room at Nimes University Hospital.

In case of hardware or software problems, a specific safety procedure has been implemented.

The export of data for analysis is conducted by a BESPIM authorized professional.

The closing of the trial including the closure of the centres is conducted in accordance with Good Clinical Practice and ICH. Medical and administrative records and CRFs are kept for the duration of the study in the service and then archived for a minimum of 30 years.

Confidentiality:

In accordance with article R.5120 of the French Public Health Code, the investigators, as well as any persons collaborating in the study, will respect medical confidentiality especially as concerns the nature of the study, the persons participating in the study, and the obtained results.

The study protocol, documentation, data, and all other information generated is held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The investigator will ensure that the anonymity of each person involved in the study is respected. On all study-related documents, the patient is identified using only a unique, 7-character identification number (C□□P□□□), and the first letter of his/her last name, the first letter of his/her first name, and his/her year of birth. A patient identification list is maintained by the investigator (and only the investigator).

Statistical methods:

The primary outcome is the change from baseline in the ADHDRS-PI at 5 months. If required for meeting normality, the ADHDRS-PI scores will be appropriately transformed (e.g. Box-Cox transformation). A Student's test will be used to compare the two groups. If the conditions for use of a Student's test are not met, a non-parametric Mann-Whitney test will be used. This analysis will be completed by a modelling analysis to take into account clustering effects. Indeed, in our study, randomization to treatment is done on an individual basis; however, the experimental and control treatments are administered to a group so that several individuals receive the intervention together by the same therapists; the observations within

the group therapy will likely be correlated within groups (clustering effect). We'll use multilevel mixed-effects models to assess the treatment effect on the primary outcome: the ADHDRS-PI score at 5 months by adjusting for cluster effects and ADHDRS-PI score at baseline.

The models will also provide valuable estimates of intra-cluster correlation coefficients for the different outcomes of our study in the context of behavioural group therapy; these data are necessary to optimize the sample size of further studies in the area of psychological research. Similar methods will be used for secondary outcomes. The temporal evolution of repeated quantitative measures (baseline, 5 months, 8 months) will be compared between groups by a mixed model for repeated longitudinal data.

As concerns the primary efficacy outcome, data missingness will probably not be random (MNAR). Multiple imputation methods will be used to replace missing data. For exploratory variables, missing data will not be replaced.

Blinding will be removed in 2 steps: analysis will be performed upon completion of the study and freezing of the database, using patient group assignments as group A versus B only. When all analyses have been performed and the final report drafted, treatment assignment to groups will be fully unblinded. The level of significance is set at $p < 0.05$ (bilateral). To control for the success of blinding, outcome assessor responses to the "guess-the-group" question will be compared to true responses using the kappa agreement coefficient.

There is no a priori reason for carrying out *per protocol* analyses in the present study. All analyses will therefore be performed on the *intention to treat* population. The statistical analysis will be described in detail before data extraction and unblinding. Any deviations, reasons for such deviations and all alternative or additional statistical analyses that may be done, will be described in the final report. The statistical analysis will be performed by the BESPIM using SAS software (SAS Institute, Cary, NC, USA) version 9.4 (or higher) or the R statistics environment (R Development Core Team 2008) version 3.3.1 (or higher).

Oversight and monitoring:

Due to the low level of risk added by this research and the lack of interim analyses, a data monitoring committee (DMC) will not be formed. A sponsor-delegated research assistant regularly visits each of the study centres during the implementation of the trial. One or more visits are carried out during the trial according to the rhythm of the inclusions and the duration of the study. All monitoring visits are accompanied by a written monitoring report (visit traceability). The present study compares two types of group therapy for parents and children. Harms are not expected in association with group therapy. All the children and parents participating in group therapy are expected to positively benefit from said therapy. No specific surveillance is required. The only procedure added for research purposes is the administration of questionnaires. Investigators agree to comply with the requirements of the sponsor and the Competent Authority in respect to audits or inspections of the study.

Adverse event reporting and harms:

Consequently, any serious adverse event occurring in a subject included in this research must be notified by the investigator to the appropriate safety system:

✓ Some children included in this protocol may be treated with Ritalin. In this case, any adverse effect likely to be due to the treatment administered or to its use must be declared to the Regional Center of Pharmacovigilance (CRPV).

✓ Any serious adverse event associated with the care must be reported by the investigator as part of the reporting obligation for serious adverse events related to care according to the procedures in effect in the institution

When the event is reported to the appropriate safety system, the investigator must specify the inclusion of the patient in a clinical research protocol, specifying the references of the research.

Auditing:

Investigators agree to comply with the requirements of the sponsor and the Competent Authority in respect to audits or inspections of the study. An audit can cover all stages of the study, from protocol development to publication of results and the classification of the data used or produced as part of the study

Ancillary and post-trial care:

The subjects included in the trial are monitored for 8 months. The monitoring of complications and adverse events is scheduled. Any patients who experience an adverse event (or not), are followed up by the investigator until complete resolution of the complication. Following study completion or end, follow-up is continued as decided by the investigator.

Protocol amendments:

Any substantial change, that is to say, any changes that might have a significant impact on the protection of persons, the conditions of validity and the results of research, on the quality and safety of the interventions tested, on interpretation of scientific documents that support the conduct of research, or the modality of conduct, will be the subject of a written amendment that is submitted by the sponsor to the CPP and the competent authority for approval prior to being implemented. Insubstantial changes, that is to say those that have no significant impact on any aspect of research whatsoever are transmitted to the CPP in order to inform the CPP of such changes.

All amendments to the protocol must be brought to the attention of all investigators involved in the research. Investigators are obliged to respect their content. Any amendment that modifies the care of patients or the benefits, harms, risks and constraints of the research is the subject of a new briefing note and a new consent form which requires the same collecting procedures as mentioned above.

Dissemination plans:

Communication of results to participants, healthcare professionals and the public will be made through scientific conferences and publications in “open-access”. Pursuant to Act No. 2002-303 of 4 March 2002, patients will be informed, upon request, of overall research results. Any written or oral communication of research results will receive prior approval from the coordinating investigator. Currently, Nimes University Hospital does not support public access to trial documents. However, should such requirements occur in association with publication submissions, the Open Science Framework will be used (https://osf.io/). All persons qualifying as authors according to the ICMJE will be asked to sign an authorship contract.

Discussion

This project is designed to test an enhanced psychotherapy for children/adolescents with ADHD. Despite the high prevalence of this disorder in childhood, most research has focused on drug treatments since the latter have shown higher efficacy in decreasing ADHD symptoms. However, several reasons justify our project: 1) drugs are associated with short- and (unknown) long-term risks and adverse effects; 2) combined therapies (psychotherapy + stimulants) have better outcomes than stimulants alone; 3) either effect (drug or psychotherapy) diminishes with time, so new therapeutic approaches with long term effects are therefore needed; 4) an increasing number of parents/professionals are reluctant to try drug treatments and require alternative approaches; and 5) the efficacy of pharmacotherapy is reduced in many cases, especially when comorbidities are present (80% of ADHD children).

To date, results for psychotherapy programs for ADHD are inconsistent although several studies have shown clinical improvements (Hodgson et al, 2014; Sonuga-Barke et al, 2013). This is probably due to heterogeneous measures and raters, small samples and varying endpoints selected in prior studies. Clarifying the efficacy of specific psychotherapies for ADHD and standardizing their practice is therefore urgently needed. In the present day, care options for ADHD children vary and are strongly influenced by psychodynamic approaches in France.

During the elaboration of the mCBT program, we have observed reductions in ADHD symptomatology and anxiety-depression scores, but also an improvement of self-esteem, emotional regulation, social integration and school results after mCBT therapy. This project will therefore implement a rigorous methodology in order to confirm preliminary results. This is an original program that integrates for the first-time multiple treatment approaches (social skills training, emotional and behavioural regulation, self-esteem, cognitive remediation and mindfulness) into a single cognitive behavioural therapy (and not separate therapies). The program also integrates mindfulness, known to reduce ADHD symptoms and behavioural problems in children when tested independently of other interventions (Cairncross & Miller 2016). Finally, the program is carried out simultaneously for children and parents (including behavioural techniques, emotional regulation and mindfulness as well), thus avoiding excessive impact on the daily life of families.

ADHD is a chronic pathology with major public health implications. Approximately 1/3 of ADHD children will not finish secondary studies, and many of them will show negative outcomes in their adult life, from unemployment or substance abuse to antisocial personality, marginalization and criminality. The validation of a high performing psychotherapeutic program, as we propose in this study, for minimizing the burden (huge personal, social and economic costs) associated with ADHD is long awaited for.

Trial status:

Currently recruiting, 171 children/family have agreed to participate in three centres: Nimes, Montpelier and Paris. Version 3.0 of this protocol was approved on 09/30/2019. Recruitment began on February 19th, 2018. The expected date to complete the recruitment is September 2021.

Declarations

Acknowledgements:

Professional writers assisted protocol drafting and article writing. Authorship follows the guidelines set by the International Committee of Medical Journal Editors (ICMJE). We thank Leonie Gazel for her help in organizing the research protocol.

Authors' Contributions:

Anne Gramond, Mocrane Abbar and Jorge Lopez-Castroman conceived and designed the study. Laetitia Crouzet, Carey Suehs and Jorge Lopez-Castroman drafted the manuscript and managed the literature searches and analyses. Anne Gramond, Pascale Fabbro-Peray and Mocrane Abbar helped to draft the manuscript. All authors revised the article critically. All authors read and approved the final manuscript. There is no one else who fulfils the criteria but has not been included as an author.

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Availability of data and materials:

Data management and statistical analysis is provided by the « Laboratoire de Biostatistique, Epidémiologie clinique, Santé Publique Innovation et Méthodologie » (BESPIM) at NUH. The conditions of transfer of all or part of the research database are decided by the research sponsor and are subject to a written contract. The data will not be publicly available.

Ethics approval and consent to participate:

The research has been implemented after a favorable opinion from the Competent Authority and Committee for the Protection of Persons (CPP TOURS - Région Centre - Ouest 1, http://cppouest1.fr, IRB n° IORG0008143 OMB : 0990-0279) and the information of the “Agence Nationale de Sécurité du Médicament et des Produits de Santé” (ANSM), in France. This is a biomedical research protocol requiring informed consent of participants. An informative letter is presented to the participant stating the purpose, the objectives and conduct of the study in accordance with current regulations and their rights to refuse to participate or leave the study at any time. Patient consent is sought and obtained before the entry thereof in the study. The investigators are responsible for correctly informing patients/subjects and obtaining their informed consent. Participant children sign a consent form adapted to their age (6-11 and 11-15 years), and their parents too. The approval of these consent forms can be found in the validation letter by the CPP.

Consent for publication:

Not applicable.

Competing interests:

The authors have no conflicts of interest related to the contents of the manuscript.

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Tables

Table 1. Structure of a typical session of Hyper mCBT program for parents.

Structure of the session	
1.	Welcome
2.	Meditation: today's interior weather
3.	Review of last session's missions
4.	Relaxation
5.	Session: the day's theme
6.	Session summary
7.	New missions
8.	Summary and missions presented in children's group

Figures

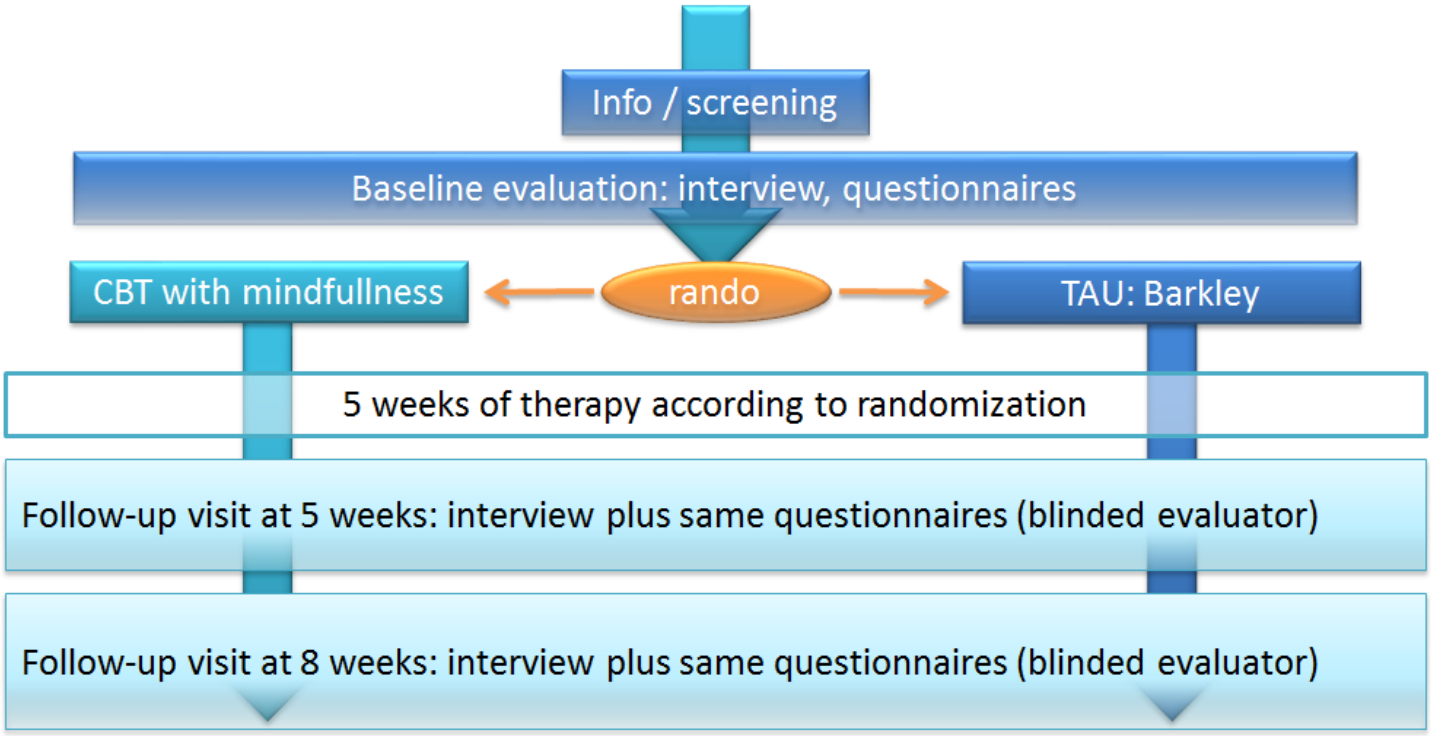

Figure 1

Base line evaluation of the study

	Screening	Enrol	Therapy	Eval-5m	Eval-8m
Time frame:	M-4 to D-2	D-14 to D-1	Day 0 to W19	W20	W32
Allowed variation:				W20 to W21	W32-W33
Information and screening					
Eligibility verification	●				
Delivery of information sheet and study presentation	●				
Interventions					
16 sessions of mCBT group therapy in the experimental arm			●		
12 sessions of Barkley group therapy in the comparator arm			●		
Evaluations with a blinded evaluator					
Signature of consent form		●			
Eligibility verification		●			
Heteroquestionnaires administered by the evaluator:					
• K-SADS-PL		●			
• CGI-S		●		●	●
• CGAS		●		●	●
• ADHDRS-PI		●		●	●
• CDI		●		●	●
Questionnaires for parents					
• ASRS		●			
• Parenting style profile		●		●	●
• PAR-DD-QoI		●		●	●
• HADS		●		●	●
• Conners for parents		●		●	●
Questionnaires for children:					
• Rosenberg questionnaire		●		●	●
• MASC		●		●	●
Questionnaire for teachers (organized by the CRT):					
• Connors for teachers		●		●	●
Randomization by a participating psychologist after baseline evaluation		●			
Safety assessments					
Recording of adverse events		●	●	●	●

Figure 2

Participant time line

Supplementary Files

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