UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA
DEPARTAMENTO DE PSIQUIATRIA

LUISA SHIGUEMI SUGAYA

Estudo sobre tratamento de crianças pré-escolares com transtorno de déficit de atenção e hiperatividade e irritabilidade

(Versão corrigida. Resolução CoPGr 6018/11, de 1 de novembro de 2011. A versão original está disponível na Biblioteca da FMUSP)

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Psiquiatria

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RESUMO

Sugaya LS. Estudo sobre tratamento de crianças pré-escolares com transtorno de déficit de atenção e hiperatividade e irritabilidade [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2023.

O transtorno de déficit de atenção e hiperatividade (TDAH) é um transtorno do neurodesenvolvimento caracterizado por um padrão persistente de desatenção e/ou hiperatividade/impulsividade que interfere no funcionamento ou desenvolvimento causando prejuízos sociais, acadêmicos e ocupacionais. Os sintomas comumente têm início nos primeiros anos de vida e apresentam um curso crônico. Ao longo da vida, o TDAH está associado a diversas condições comórbidas, como transtornos disruptivos, transtornos de ansiedade, transtornos de humor, entre outros. A irritabilidade é um sintoma frequente entre indivíduos com TDAH, principalmente entre crianças pré-escolares, que apresentam imaturidade no processo de regulação emocional. Apesar da relevância da identificação e do tratamento precoce de crianças com TDAH, há importantes questões não respondidas sobre a eficácia das diferentes modalidades de tratamento para crianças pré-escolares, bem como sobre a avaliação de irritabilidade neste momento do desenvolvimento. Assim, esta tese buscou abordar essas lacunas do conhecimento. Para tanto, foram realizados 3 estudos. O primeiro foi o 'Estudo Mappa', um ensaio clínico randomizado, duplo-cego, controlado por placebo e controlado por treinamento parental comportamental-*sham* (TPC-*sham*), realizado com objetivo de determinar a segurança e eficácia de metilfenidato e treinamento parental comportamental (TPC) por 8 semanas na redução de sintomas de TDAH e na melhora do funcionamento global em crianças pré-escolares. Adicionalmente, foi realizada uma revisão sistemática e meta-análise com o objetivo de sintetizar as evidências disponíveis sobre a eficácia e aceitabilidade do uso de estimulantes nesta população. Por fim, devido à falta de instrumentos destinados a avaliação de irritabilidade em crianças pré-escolares traduzidos para o português, foi realizado um estudo de validação da escala *Affective Reactivity Index* (ARI) em duas amostras de crianças pré-escolares brasileiras: uma amostra escolar e uma amostra clínica de crianças com TDAH. Para o 'Estudo Mappa', 153 crianças de 3-5 anos com TDAH foram randomizadas igualmente entre três grupos (1:1:1): metilfenidato + TPC-

sham, placebo + TPC e placebo + TPC-*sham*. Somente 9 crianças descontinuaram o tratamento, nenhuma delas devido a eventos adversos. Todos os participantes foram incluídos nas análises por intenção de tratamento. Os resultados demostraram que metilfenidato é eficaz para reduzir sintomas de TDAH (TE=-0,55) e melhorar o funcionamento global (TE=0,80) enquanto o TPC é eficaz para melhorar o funcionamento global (TE=0,56). Análises de desfechos secundários também mostraram que metilfenidato melhora a performance em testes cognitivos de atenção, enquanto TPC reduz irritabilidade. A revisão sistemática incluiu 5 ensaios clínicos randomizados, duplo-cegos e a meta-análise demonstrou que o uso de estimulantes reduz sintomas de TDAH (TE=-0,59), corroborando os achados do 'Estudo Mappa'. Os resultados do estudo de validação da escala ARI indicaram adequada validade e confiabilidade na avaliação de crianças pré-escolares, possibilitando seu uso para esta faixa etária. O conjunto de estudos desta tese aponta para a eficácia e segurança de estimulantes na redução dos sintomas de TDAH e para efeitos específicos das duas modalidades de tratamento em desfechos secundários. Assim, contribui para a tomada de decisão clínica e para a formulação de diretrizes de tratamento. E contribui para o avanço do conhecimento e a realização de novas pesquisas sobre o TDAH na idade pré-escolar.

Palavras-chave: Transtorno de déficit de atenção e hiperatividade. Pré-escolar. Metilfenidato. Terapia comportamental. Irritabilidade. Ensaios clínicos. Metanálise. Psicometria.

ABSTRACT

Sugaya LS. Study on the treatment of preschool children with attention deficit hyperactivity disorder and irritability [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2023.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattention, hyperactivity, and impulsivity that interferes with functioning or development, causing social, academic, and occupational impairments. The symptoms typically emerge in the first few years of life and have a chronic course. Throughout the lifespan, ADHD is associated with several comorbid conditions, such as disruptive behavior disorders, anxiety disorders, mood disorders and others. Irritability is a frequent symptom among individuals affected by ADHD, especially among preschoolers, whose process of emotional regulation is immature. Despite the importance of early identification and treatment of children with ADHD, there are important questions that remain unanswered about the efficacy of different treatment modalities for preschoolers, as well as about the assessment of irritability at this stage of development. Thus, this thesis sought to address these gaps in knowledge. Therefore, three studies were carried out. The first is the ‘Mappa Study’, an 8-week randomized, double-blind, placebo- and sham behavioral parent training-controlled clinical trial aimed to investigate the safety and efficacy of methylphenidate and behavioral parenting training (BPT) in reducing ADHD symptoms and improving global functioning in preschool children. Additionally, a systematic review and meta-analysis were conducted to synthesize the available evidence on the efficacy and acceptability of the use of stimulants in this population. Finally, due to the lack of instruments to assess irritability in preschool children translated into Brazilian Portuguese, a study was conducted to validate the Affective Reactivity Index (ARI) scale in two samples of Brazilian preschoolers: a school-based sample and a clinical sample of children with ADHD. For the ‘Mappa Study’, 153 children aged 3-5 years with ADHD were randomized equally into three groups (1:1:1): methylphenidate + sham-BPT, placebo + BPT, and placebo + sham-BPT. Only 9 children discontinued treatment, none of them due to adverse events. All participants were included in intention-to-treat analyses. The results showed that methylphenidate reduced ADHD

symptoms (ES=-0,55) and improved global functioning (ES=0,80), while BPT improved global functioning (ES=0,56). The systematic review included 5 randomized, double-blind, clinical trials and the meta-analysis demonstrated that stimulants are efficacious in reducing ADHD symptoms (ES=-0.59), supporting the findings of the 'Mappa Study'. The results of the ARI validation study indicate adequate validity and reliability in the assessment of irritability in preschool children, enabling its use for this age group. The set of studies in this thesis points to the efficacy and safety of stimulants in reducing ADHD symptoms and to specific effects of the two treatment modalities on secondary outcomes. Thus, it contributes to clinical decision-making and to the formulation of treatment guidelines. It also contributes to the development of new studies on ADHD in preschool.

Keywords: Attention deficit and hyperactivity disorder. Child, preschool. Methylphenidate. Behavioral therapy. Irritability. Clinical trials. Meta-analysis. Psychometrics.

SUMÁRIO

1 INTRODUÇÃO

O estudo sobre tratamento de crianças pré-escolares com transtorno de déficit de atenção e hiperatividade (TDAH) se constituiu como foco desta tese a partir da experiência clínica da candidata no Programa de Diagnóstico e Intervenção Precoce (ProDIP) do Instituto de Psiquiatria da Universidade de São Paulo (IPq – HCFMUSP) ao longo de 5 anos.

De acordo com o Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-5, 2013; p. 61), o TDAH é um transtorno do neurodesenvolvimento caracterizado por "um padrão persistente de desatenção e/ou hiperatividade-impulsividade que interfere no funcionamento ou no desenvolvimento" [1], causando prejuízos em diversas áreas da vida do indivíduo. Os sintomas do TDAH comumente têm início na infância e apresentam um curso crônico [2]. Em crianças pré-escolares, o TDAH está associado a prejuízos na aprendizagem, prejuízos nas relações com pares e maior risco de acidentes [3,4]. Ao longo da vida, são documentados prejuízos sociais, acadêmicos, ocupacionais, maiores taxas de uso de substâncias, acidentes não intencionas, encarceramento e maior mortalidade [3,5–7]. Assim, medidas voltadas para identificação e tratamento precoce do TDAH são fundamentais, uma vez que intervenções efetivas podem alterar a trajetória de desenvolvimento destas crianças e prevenir diversos desfechos negativos.

No entanto, faltam evidências na literatura que possam orientar o tratamento de crianças pré-escolares com TDAH. Atualmente, diretrizes internacionais recomendam o uso treinamento parental comportamental (TPC) como primeira linha de tratamento, seguido do uso estimulantes para as crianças que mantiverem sintomas ou prejuízos significativos [8,9]. Contudo, há um número restrito de ensaios clínicos conduzidos com metodologia adequada que tenham avaliado o uso de estimulantes nesta população. Ainda, meta-análises encontram efeito significativo do TPC sobre os sintomas de TDAH somente quando estes desfechos são relatados por pais que não são cegos para a alocação do tratamento [10,11]. Além disso, dificuldades relacionadas à implementação do TPC – como disponibilidade de terapeutas treinados, limitações econômicas, ou disponibilidade de os pais participarem da intervenção – limitam o acesso a esta modalidade de tratamento. De forma que, nos EUA, aproximadamente 75% das crianças pré-escolares com TDAH são tratadas com

medicamentos, em sua maioria *off-label*, e somente cerca de 55% recebem intervenções psicoterápicas [12]. Há, portanto, a necessidade de novos ensaios clínicos randomizados, duplo-cegos que avaliem a eficácia e segurança de estimulantes e TPC para o tratamento de crianças pré-escolares com TDAH e que controlem para efeitos não específicos de ambos os tratamentos.

Nesse contexto, foi realizado o 'Estudo Mappa', um ensaio clínico randomizado, duplo-cego, controlado por placebo e controlado por treinamento parental comportamental-*sham* (TPC-*sham*), que avaliou o uso de metilfenidato e TPC no tratamento de crianças pré-escolares com TDAH. Neste estudo, foram comparados 3 grupos de tratamento: metilfenidato + TPC-*sham*, placebo + TPC e placebo + TPC-*sham*. O principal objetivo do estudo foi avaliar a segurança e a eficácia de metilfenidato e TPC na redução da frequência e gravidade dos sintomas de TDAH e na melhora do funcionamento global. Como objetivo secundários, foram avaliados os efeitos dos tratamentos na redução de comportamentos disruptivos e irritabilidade e na performance em um teste computadorizado que avalia atenção e impulsividade,

A irritabilidade foi incluída como um desfecho secundário por este ser um sintoma frequente em crianças pré-escolares com TDAH, de grande relevância clínica, e com poucas evidências a respeito do seu tratamento. Embora meta-análises já tenham avaliado o efeito de TPC sobre problemas de conduta (i.e., sintomas do transtorno de oposição desafiante e do transtorno de conduta) [10,11], esses estudos não avaliaram o efeito do TPC especificamente sobre irritabilidade. Ainda, a despeito de evidências mostrando que estimulantes reduzem irritabilidade em crianças escolares com TDAH [13,14], ensaios clínicos que avaliaram o uso de estimulantes em crianças pré-escolares com TDAH não incluíram irritabilidade como um desfecho. Em contrapartida, estes ensaios clínicos indicam que, em crianças pré-escolares, irritabilidade pode ser um evento adverso clinicamente significativo [15–17]. Dessa forma, evidências sobre os efeitos do TPC e do uso de metilfenidato sobre irritabilidade também são necessárias e relevantes para o tratamento de crianças pré-escolares com TDAH.

Adicionalmente, com o objetivo de aprofundar a discussão sobre o tratamento farmacológico de crianças pré-escolares e considerando a publicação recente de novos ensaios clínicos, foi conduzida uma revisão sistemática e meta-análise com

objetivo de revisar e sintetizar as evidências sobre a eficácia e aceitabilidade do uso de estimulantes para tratamento de crianças pré-escolares com TDAH.

Por fim, durante o desenvolvimento do protocolo de pesquisa utilizado no 'Estudo Mappa', verificou-se a falta de instrumentos destinados a avaliação de irritabilidade traduzidos para o português do Brasil e validados em amostras de crianças pré-escolares. Dessa forma, a pesquisa sobre instrumentos que avaliam irritabilidade se apresentou como um segundo foco de interesse, desenvolvido de forma paralela, mas articulada à realização do 'Estudo Mappa'.

Nesse contexto, a candidata realizou doutorado sanduíche na *Section on Mood Dysregulation and Neuroscience* (SMDN), no *National Institute of Mental Health* (NIMH), sob supervisão da Dra. Ellen Leibenluft. A Dra. Leibenluft é uma das maiores autoridades mundiais no estudo de irritabilidade na infância e adolescência, tendo sido autora dos critérios que definiram a 'desregulação grave do humor', os quais deram origem à nova categoria diagnóstica do transtorno disruptivo de desregulação do humor (TDDH), incluída no DSM-5. Durante o período de doutorado sanduíche, foi realizado o estudo sobre a validação da escala *Affective Reactivity Index* (ARI) em 2 amostras de crianças pré-escolares brasileiras. A ARI [18] é uma escala que se destaca por ser breve, ter boas propriedades psicométricas, ser amplamente utilizada e já ter sido traduzida para diversas línguas, incluindo o português do Brasil [19]. No entanto, a ARI foi desenvolvida para avaliação de crianças escolares e adolescentes e seu uso para avaliação de crianças em idade pré-escolar não havia sido previamente testado. Este estudo foi desenvolvido em colaboração com o Dr. Argyris Stringaris, um dos autores da escala. Adicionalmente, foi feita a tradução e adaptação da *Multidimensional Assessment Profile of Disruptive Behavior* (MAP-DB) para o português do Brasil, em colaboração com a Dra. Lauren Wackschlag, autora da escala. A MAP-DB é uma escala multidimensional cuja a dimensão de descontrole emocional (*Temper Loss*) é utilizada na literatura como medida de irritabilidade [20,21]. Um diferencial deste instrumento é que ele investiga a ocorrência de um amplo espectro de comportamentos e com diferentes níveis de gravidade, incluindo tanto comportamentos normativos como comportamentos atípicos para crianças pré-escolares.

Além de contribuir para o estudo da irritabilidade precoce no Brasil, a validação da versão em português da escala ARI em amostras de crianças pré-escolares e a

tradução da escala MAP-DB podem contribuir para o desenvolvimento de pesquisas transculturais e trazer avanços importantes para o campo, uma vez que, atualmente, a maior parte das pesquisas se concentra nos Estados Unidos. Neste sentido, a candidata foi convidada para integrar o *Steering Committe* do recém criado *Cross-Cultural Consortium on Irritability*, que conta, atualmente com 95 investigadores de 20 países.

Dessa forma, nesta tese, são apresentados os 3 estudos desenvolvidos durante o doutorado: 1) o 'Estudo Mappa', ensaio clínico randomizado, duplo-cego, controlado por placebo e treinamento parental comportamental-*sham* avaliando a segurança e eficácia do uso de metilfenidato e treinamento parental no tratamento de crianças pré-escolares com TDAH; 2) a revisão sistemática e meta-análise sobre a eficácia e aceitabilidade do uso de estimulantes para tratamento de crianças pré-escolares com TDAH, e 3) o estudo de validação da escala *Affective Reactivity Index* (ARI) em 2 amostras de crianças pré-escolares brasileiras.

2. REVISÃO TEÓRICA

2.1 Transtorno de Déficit de Atenção e Hiperatividade (TDAH)

De acordo com o Manual diagnóstico e estatístico de transtornos mentais (DSM-5, 2013; p. 61), O Transtorno de Déficit de Atenção e Hiperatividade (TDAH) é um transtorno do neurodesenvolvimento caracterizado por um "um padrão persistente de desatenção e/ou hiperatividade-impulsividade que interfere no funcionamento e no desenvolvimento" [1]. Os critérios diagnósticos definidos pelo DSM-5 estão descritos abaixo:

Critérios Diagnósticos do Transtorno de Déficit de Atenção/Hiperatividade

A. Um padrão persistente de desatenção e/ou hiperatividade-impulsividade que interfere no funcionamento e no desenvolvimento, conforme caracterizado por (1) e/ou (2):

1. **Desatenção:** Seis (ou mais) dos seguintes sintomas persistem por pelo menos seis meses em um grau que é inconsistente com o nível do desenvolvimento e têm impacto negativo diretamente nas atividades sociais e acadêmicas/profissionais:

a. Frequentemente não presta atenção em detalhes ou comete erros por descuido em tarefas escolares, no trabalho ou durante outras atividades (p. ex., negligencia ou deixa passar detalhes, o trabalho é impreciso).
b. Frequentemente tem dificuldade de manter a atenção em tarefas ou atividades lúdicas (p. ex., dificuldade de manter o foco durante aulas, conversas ou leituras prolongadas).
c. Frequentemente parece não escutar quando alguém lhe dirige a palavra diretamente (p. ex., parece estar com a cabeça longe, mesmo na ausência de qualquer distração óbvia).
d. Frequentemente não segue instruções até o fim e não consegue terminar trabalhos escolares, tarefas ou deveres no local de trabalho (p. ex., começa as tarefas, mas rapidamente perde o foco e facilmente perde o rumo).
e. Frequentemente tem dificuldade para organizar tarefas e atividades (p. ex., dificuldade em gerenciar tarefas sequenciais; dificuldade em manter materiais e objetos pessoais em ordem; trabalho desorganizado e desleixado; mau gerenciamento do tempo; dificuldade em cumprir prazos).
f. Frequentemente evita, não gosta ou reluta em se envolver em tarefas que exijam esforço mental prolongado (p. ex., trabalhos escolares ou lições de casa; para adolescentes mais velhos e adultos, preparo de relatórios, preenchimento de formulários, revisão de trabalhos longos).
g. Frequentemente perde coisas necessárias para tarefas ou atividades (p. ex., materiais escolares, lápis, livros, instrumentos, carteiras, chaves, documentos, óculos, celular).
h. Com frequência é facilmente distraído por estímulos externos (para adolescentes mais velhos e adultos, pode incluir pensamentos não relacionados).
i. Com frequência é esquecido em relação a atividades cotidianas (p. ex., realizar tarefas, obrigações; para adolescentes mais velhos e adultos, retornar ligações, pagar contas, manter horários agendados).

1. **Hiperatividade e impulsividade:** Seis (ou mais) dos seguintes sintomas persistem por pelo menos seis meses em um grau que é inconsistente com o nível do desenvolvimento e têm impacto negativo diretamente nas atividades sociais e acadêmicas/profissionais:

a. Frequentemente remexe ou batuca as mãos ou os pés ou se contorce na cadeira.
b. Frequentemente levanta da cadeira em situações em que se espera que permaneça sentado (p. ex., sai do seu lugar em sala de aula, no escritório ou em outro local de trabalho ou em outras situações que exijam que se permaneça em um mesmo lugar).
c. Frequentemente corre ou sobe nas coisas em situações em que isso é inapropriado.
d. Com frequência é incapaz de brincar ou se envolver em atividades de lazer calmamente.
e. Com frequência "não para", agindo como se estivesse "com o motor ligado" (p. ex., não consegue ou se sente desconfortável em ficar parado por muito tempo, como em restaurantes, reuniões; outros podem ver o indivíduo como inquieto ou difícil de acompanhar).
f. Frequentemente fala demais.
g. Frequentemente deixa escapar uma resposta antes que a pergunta tenha sido concluída (p. ex., termina frases dos outros, não consegue aguardar a vez de falar).
h. Frequentemente tem dificuldade para esperar a sua vez (p. ex., aguardar em uma fila).
i. Frequentemente interrompe ou se intromete (p. ex., mete-se nas conversas, jogos ou atividades; pode começar a usar as coisas de outras pessoas sem pedir ou receber permissão; para adolescentes e adultos, pode intrometer-se em ou assumir o controle sobre o que outros estão fazendo).

B. Vários sintomas de desatenção ou hiperatividade-impulsividade estavam presentes antes dos 12 anos de idade.
C. Vários sintomas de desatenção ou hiperatividade-impulsividade estão presentes em dois ou mais ambientes (p. ex., em casa, na escola, no trabalho; com amigos ou parentes; em outras atividades).
D. Há evidências claras de que os sintomas interferem no funcionamento social, acadêmico ou profissional ou de que reduzem sua qualidade.
E. Os sintomas não ocorrem exclusivamente durante o curso de esquizofrenia ou outro transtorno psicótico e não são mais bem explicados por outro transtorno mental (p. ex., transtorno do humor, transtorno de ansiedade, transtorno dissociativo, transtorno da personalidade, intoxicação ou abstinência de substância).

Determinar o subtipo:
Apresentação combinada: Se tanto o Critério A1 (desatenção) quanto o Critério A2 (hiperatividade-impulsividade) são preenchidos nos últimos 6 meses.
Apresentação predominantemente desatenta: Se o Critério A1 (desatenção) é preenchido, mas o Critério A2 (hiperatividade-impulsividade) não é preenchido nos últimos 6 meses
Apresentação predominantemente hiperativa/impulsiva: Se o Critério A2 (hiperatividade-impulsividade) é preenchido, e o Critério A1 (desatenção) não é preenchido nos últimos 6 meses.

Fonte: American Psychiatric Association (2013, p. 59-60)

De acordo com meta-análise publicada em 2007, que incluiu mais de cem estudos de todo o mundo, a prevalência do TDAH em crianças e adolescentes é de aproximadamente 5.3% (95% CI: 5.01–5.56), com uma predominância de casos entre meninos [22]. A etiologia do TDAH é multifatorial, envolvendo fatores genéticos, neurobiológicos e ambientais que interagem entre si através de mecanismos psicopatológicos complexos [23]. O TDAH apresenta uma alta agregação familiar e seu coeficiente de herdabilidade é estimado em 70-80%. Os estudos genéticos indicam que o TDAH apresenta uma arquitetura poligênica que envolve tanto variantes comuns como variantes raras [24,25]. Além disso, fatores genéticos relacionados ao

TDAH são compartilhados com outros transtornos psiquiátricos e traços psicopatológicos, como transtorno do espectro autista, transtorno afetivo bipolar, depressão, prejuízos cognitivos, irritabilidade e problemas de conduta [25].

Diversos fatores de risco ambientais já foram associados ao TDAH. No entanto, não está claro se se tratam de relações causais ou se fatores genéticos explicam essas associações [2]. Estudos indicam que associações entre o TDAH e fatores de risco, como exposição intrauterina ao tabaco, podem ser atribuídas, pelo menos em parte, a fatores genéticos confundidores [26]. Nesse contexto, fatores de risco associados de maneira mais consistente ao TDAH incluem: prematuridade, baixo peso ao nascer e privação extrema em períodos precoces do desenvolvimento [27–29].

Em relação aos fatores neurobiológicos, já foram identificadas alterações em estruturas corticais e subcorticais [30,31], assim como alterações funcionais em diversos circuitos cerebrais, como circuitos frontoparietais, frontoestriatais, mesocorticolímbicos e circuitos que compõe a *default mode network* e a *cognitive control network* [32]. Estudos longitudinais também indicam que o TDAH está relacionado a um atraso na maturação cerebral [33,34]. Adicionalmente, pacientes com TDAH apresentam alterações cognitivas variadas que se manifestam de forma heterogênea, incluindo déficits em funções executivas (como memória operacional, controle inibitório, vigilância e planejamento), resposta a recompensa, linguagem, *span* de memória, velocidade de processamento, controle motor e processamento de informação temporal [2].

Do ponto de vista clínico, os sintomas do TDAH costumam surgir durante a infância e apresentam um curso crônico, causando prejuízos que se estendem até idade adulta [35,36]. Ao longo da vida, o TDAH está associado a diversos desfechos negativos, incluindo prejuízos sociais, acadêmicos, ocupacionais, econômicos, uso de substâncias, acidentes não intencionas, encarceramento e maior mortalidade [3,5–7], o que corrobora a necessidade de tratamentos eficazes.

Em termos de tratamento, para crianças escolares, adolescentes e adultos, o uso de estimulantes já se mostrou eficaz e seguro para a redução dos sintomas de TDAH [37]. Estudos fármaco-epidemiológicos também sugerem que o uso destas medicações está associado a redução de eventos negativos, como acidentes, transtorno relacionado ao uso de substâncias e envolvimento com o crime [6,38,39]. No

entanto, ainda faltam evidências consistentes que possam informar o tratamento de crianças pré-escolares, como será demonstrado nas seções a seguir.

2.2 TDAH e pré-escolares

O termo pré-escolar é comumente utilizado para se referir a crianças de 3 a 5 anos de idade. Neste período, ocorrem mudanças comportamentais significativas que refletem etapas importantes do desenvolvimento da linguagem e funções executivas. É nesta fase que os primeiros sintomas do TDAH começam a ser observados. Estima-se que a prevalência do TDAH em pré-escolares seja de 2.7–4.3% [40].

Em crianças pré-escolares com TDAH, os sintomas de hiperatividade/impulsividade costumam ser mais evidentes e os sintomas de desatenção menos proeminentes do que em crianças em idade escolar. Essa variação no padrão de sintomas acompanha processos relacionados ao desenvolvimento infantil e reflete-se na baixa estabilidade da apresentação do TDAH durante a transição entre a idade pré-escolar e escolar. Apesar da variação em sua apresentação, o diagnóstico de TDAH em pré-escolares já se mostrou válido e estável [41]. Estudos mostram que a maior parte das crianças pré-escolares com TDAH mantém o diagnóstico na idade escolar [42]. Gravidade e pervasividade dos sintomas, status socioeconômico, educação materna e psicopatologia parental são alguns dos fatores associados à persistência do quadro [35].

Em termos de prejuízos, crianças pré-escolares com TDAH são mais frequentemente descritas como disruptivas e sem controle, sofrem mais rejeição por pares, apresentam pior desenvolvimento acadêmico e maior risco de acidentes [3,4]. Dificuldades enfrentadas neste período podem afetar a autoestima e o senso de eficácia da criança e ter consequências a longo prazo, com prejuízos cumulativos. Estes achados reforçam a importância da identificação precoce e do tratamento adequado.

2.2.1 Tratamento para crianças com TDAH em idade pré-escolar

Atualmente, diretrizes internacionais recomendam treinamento parental comportamental (TPC) como primeira linha de tratamento para as crianças pré-escolares com TDAH [8,9]. O uso de medicamentos é reservado para as crianças que

mantiverem sintomas ou prejuízos significativos. No entanto, faltam evidências robustas que suportem estas recomendações.

2.2.1.1 Tratamento farmacológico para crianças pré-escolares com TDAH

Embora diversos estudos avaliando o uso de estimulantes no tratamento de crianças pré-escolares com TDAH já tenham sido publicados, a maior parte deles apresenta limitações metodológicas significativas, como tamanhos amostrais pequenos, inclusão de pacientes com outros transtornos do neurodesenvolvimento, tempo curto de tratamento, falta de grupo controle, ou ausência de cegamento [43,44].

Assim, desde a sua publicação, o estudo *Preschool ADHD Treatment Study* (PATS) [15] é considerado a melhor evidência disponível sobre o uso de metilfenidato de liberação imediata em crianças pré-escolares com TDAH. O PATS é um ensaio clínico multicêntrico que incluiu crianças de 3 até 5 anos e meio de idade e contou com diversas fases: a) treinamento parental comportamental (n=279), b) ensaio aberto para avaliação de segurança do uso de metilfenidato (n=183), c) ensaio randomizado duplo-cego *crossover* de 5 semanas com diferentes doses (i.e., 1,25, 2,5, 5,0, ou 7,5 mg três vezes ao dia) de metilfenidato ou placebo para estabelecer a 'melhor dose' (n=165), d) ensaio randomizado duplo-cego controlado com 2 grupos em paralelo comparando a 'melhor dose' de metilfenidato (estabelecida na fase de crossover) e placebo (n=114), e e) uma fase aberta de manutenção por 10 meses (n=140).

Na fase de *crossover*, foram observados efeitos significativos do metilfenidato nas doses de 2,5, 5,0 e 7,5mg três vezes ao dia, comparados com placebo. Na média, a melhor dose foi de 14,2 $\pm$ 8,1mg (0,7 $\pm$ 0,4 mg/kg/dia). No ensaio paralelo, utilizando a melhor dose, 21% dos participantes que utilizaram metilfenidato e 13% dos participantes que receberam placebo atingiram o critério de remissão dos sintomas, sem diferença significativa entre os grupos. No entanto, em análises post-hoc por intenção de tratamento, observou-se uma redução significativa dos sintomas de TDAH no grupo que recebeu metilfenidato versus placebo – avaliado pela escala SNAP-IV respondida por pais e professores – com tamanhos de efeito (TE) de 0,48, 0,52 e 0,87 para as doses de 2,5, 5,0 e 7,5mg três vezes ao dia, respectivamente.

No estudo PATS, os eventos adversos reportados com maior frequência foram: insônia, comportamentos/pensamentos repetitivos, diminuição do apetite, ataques de

raiva/irritabilidade [45]. Ao longo do estudo, 21 crianças (11%) descontinuaram o tratamento devido a eventos adversos e 9 o fizeram devido sintomas de irritabilidade/emotividade [45]. Ao todo, ocorreram 8 eventos adversos que necessitaram de hospitalização. Destes, somente um caso de crise convulsiva foi caracterizado como possivelmente associado ao uso do metilfenidato. Oito participantes apresentaram pressão alta em uma ocasião [45]. Além disso, ao final dos 10 meses da fase de manutenção, diminuição da velocidade de crescimento e do ganho de peso foram relacionadas ao tratamento com medicação [46].

Estes dados indicam que o metilfenidato é efetivo para reduzir sintomas de TDAH. No entanto, os tamanhos de efeito foram menores e os eventos adversos foram mais comuns do que aqueles encontrados em estudos com crianças escolares e adolescentes[15]. Entre as principais limitações do estudo PATS estão um desenho metodológico com múltiplas fases e uma alta taxa de atrito, que pode ter influenciado os resultados do estudo, além de um protocolo de ajuste de doses complexo e de difícil implementação na prática clínica.

Apenas nos últimos 3 anos foram publicados outros dois ensaios clínicos duplo-cegos randomizados avaliando o uso de estimulantes de liberação prolongada comparados a placebo para o tratamento de crianças de 4-6 anos de idade com TDAH. O primeiro deles [17] foi um estudo multifásico que incluiu treinamento parental, uma fase *open-label* para ajuste de dose (6 semanas) e uma fase duplo-cego comparando a melhor dose com placebo (2 semanas). A fase final inclui 90 crianças e as análises demonstraram a eficácia do uso de metilfenidato de liberação prolongada na redução de sintomas de TDAH, com tamanho de efeito de 1,1. Os eventos adversos mais comuns neste estudo foram diminuição de apetite, redução de peso, insônia, hipertensão, alteração emocionais e labilidade afetiva. Somente um evento adverso grave foi relatado, um quadro infeccioso não relacionado ao tratamento. No segundo estudo, Childress et al. (2022) [16] avaliaram o uso de diferentes doses de lisdexanfentamina (10, 20, 30 mg) durante 6 semanas de tratamento. As análises agrupando os 3 grupos de tratamento ativo (n=107) e comparando com placebo (n=45) demonstraram a eficácia do uso da medicação na redução de sintomas de TDAH, com tamanho de efeito de 0,43. Eventos adversos foram mais frequentes entre crianças que receberam a dose de 30mg/dia de

lisdexanfetamina. Os eventos adversos mais comuns foram diminuição de apetite e irritabilidade. Nenhum evento adverso grave foi relatado.

2.2.1.2 Treinamento parental comportamental (TPC) para crianças pré-escolares com TDAH

A maior parte dos programas de treinamento parental comportamental (TPC) foram elaborados a partir do modelo desenvolvido por Constance Hanf (1969), baseado na teoria dos sistemas familiares, princípios de aprendizagem social e condicionamento operante [35]. Estes programas ensinam diferentes técnicas comportamentais, como reforçar positivamente comportamentos desejáveis, ignorar comportamentos inadequados, aplicar consequências construtivas em respostas a comportamentos indesejáveis mais graves, e têm como objetivo reduzir comportamentos disruptivos, melhorar práticas parentais, e melhorar a qualidade da interação entre pais e filhos. De forma geral, estes programas não são específicos para o tratamento de crianças com TDAH e se destinam a crianças com comportamentos disruptivos, como no caso dos programas *Incredible Years*, *Helping the Noncompliant Child (HNC)*, e *Triple P Parenting Program* [35].

O *New Forest Parenting Program (NFPP)* é uma exceção, pois foi desenvolvido especificamente para o tratamento de crianças com TDAH. Além de abordar práticas parentais, o NFPP tem como objetivo melhorar habilidades de autorregulação associadas ao TDAH [47]. No entanto, um ensaio clínico conduzido por Abikoff et al. [48] comparou o *NFPP* e o *HNC* com um grupo em lista de espera e não observou diferenças entre os dois programas na redução de sintomas de TDAH. Os resultados favoreceram o HNC em relação a alguns desfechos como agressividade, práticas parentais e stress parental.

Como salientado anteriormente, embora ensaios clínicos randomizados tenham identificado efeitos positivos dos programas TPC, meta-análise que avaliou o uso de TPC para crianças de 2.5-6 anos de idade com diagnóstico ou sintomas de TDAH encontrou efeito significativo do TPC sobre os sintomas de TDAH somente quando os desfechos foram relatados pelos pais não cegos para a alocação do tratamento [11]. Nesta meta-análise, somente o efeito do TPC sobre parentalidade negativa permaneceu significativo quando medido por avaliadores independentes.

Estes achados não foram moderados pelo tipo de programa, modalidade de intervenção ou status diagnóstico. Resultado semelhante foi encontrado em meta-análise que incluiu estudos com crianças de 3-18 anos com TDAH [10]. No entanto, nesta meta-análise, tanto os efeitos sobre parentalidade como os efeitos sobre problemas de conduta permaneceram significativos quando avaliados por informantes cegos. Embora estes dados questionem a eficácia do TPC como um tratamento específico para os sintomas do TDAH, é importante considerar que práticas parentais e problemas de conduta são desfechos clinicamente relevantes para estes pacientes.

2.3 TDAH, comportamentos disruptivos e irritabilidade

De acordo com o DSM-5 (2013, p. 461), os comportamentos disruptivos se caracterizam por serem "comportamentos que violam direitos básicos de terceiros e/ou colocam o indivíduo em conflito significativo com normas sociais ou figuras de autoridade" [1]. Eles abrangem uma grande variedade de manifestações, incluindo: humor irritável, ataques de raivas, desobediência, comportamentos agressivos, vandalismo, roubo e graves violações de regras. Assim como os sintomas de TDAH, estes comportamentos costumam se iniciar precocemente e estão associados a diversos desfechos negativos ao longo da vida [49].

No DSM-5 e na 11ª revisão da Classificação Internacional de Doenças (CID-11), estes comportamentos são descritos como sintomas do transtorno de oposição desafiante (TOD) e do transtorno de conduta (TC) [1,50]. Embora o TDAH seja classificado como um transtorno do neurodesenvolvimento e TOD/TC sejam classificados como transtornos disruptivos, estes três transtornos apresentam uma proximidade fenotípica e etiológica e frequentemente coocorrem [51–53]. Estudos epidemiológicos mostram que aproximadamente 30-40% das crianças pré-escolares com TDAH apresentam o diagnóstico ou sintomas de transtorno de oposição desafiante (TOD) [51,52]. Por conta disso, diversos estudos que avaliam o tratamento de pacientes com TDAH incluem os comportamentos disruptivos como desfechos secundários [48,54]. Nesse contexto, estes comportamentos são comumente avaliados em conjunto sob construtos como 'sintomas de oposição' ou 'problemas de conduta' [10,55,56].

No entanto, já existe um consenso de que as abordagens categoriais não capturam adequadamente o caráter heterogêneo e dimensional dos comportamentos disruptivos. Estudos longitudinais demonstram que as diferentes dimensões comportamentais apresentam trajetórias distintas ao longo do desenvolvimento [57] e estão associados a diferentes desfechos clínicos [58]. Stringaris et al. (2009) [58] e Krieger et al. (2013) [59] já mostraram que o TOD é composto por 3 dimensões de sintomas: irritabilidade, comportamento opositor/desafiador e comportamento vingativo; e que cada um dessas dimensões está, longitudinalmente, associadas a desfechos distintos (i.e., ansiedade e depressão, TDAH e problemas de conduta com limitada emoção pró-social, respectivamente) [58,59]. Também já existem evidências de que diferentes dimensões comportamentais podem estar associadas a fatores etiológicos específicos. Estudos com pares de gêmeos mostram que fatores genéticos distintos estão relacionados a comportamentos agressivos e violação de regras (não violentas) [60]. Estudos de neuroimagem funcional indicam que irritabilidade e limitada emoção pró-social estão associados a diferentes alterações na atividade cerebral [49]. Em contrapartida, em consonância com propostas como a do *Research Domain Criteria* (RDoC), abordagens transdiagnósticas mostram que traços, como impulsividade [61] e irritabilidade [62], são compartilhados por diferentes transtornos psiquiátricos.

Dessa forma, estudos que investiguem as diferentes dimensões comportamentais são necessários para avançarmos o conhecimento em relação a caracterização fenotípica de cada uma delas, para ampliarmos o conhecimento sobre mecanismos subjacentes e para que intervenções mais específicas e efetivas sejam desenvolvidas. Dentre as diferentes dimensões de comportamentos disruptivos, as pesquisas sobre irritabilidade e sobre a associação entre TDAH e irritabilidade têm ganhado destaque na literatura por sua importância clínica e pelos avanços científicos significativos realizados nas últimas décadas, como mostra a revisão da literatura.

2.3.1 TDAH e Irritabilidade

Atualmente, a irritabilidade é definida como uma maior tendência a manifestar raiva em comparação com outras crianças no mesmo estágio do desenvolvimento [63]. Suas principais manifestações clínicas incluem: ataques de raivas, humor irritável e comportamentos agressivos reativos. Entre os pacientes com TDAH, sintomas de

irritabilidade são frequentes, com taxas que variam de 25-50% [64–68]. Em amostras de pacientes com sintomas graves de irritabilidade, como os pacientes com desregulação grave do humor ou transtorno disruptivo da desregulação do humor (TDDH), cerca de 80% apresentam diagnóstico de TDAH [69]. Além disso, em crianças ou adolescentes com TDAH, sintomas de irritabilidade causam um impacto negativo significativo e estão associados a maior gravidade dos sintomas de TDAH, ocorrência de comorbidades psiquiátricas – incluindo transtornos externalizantes e internalizantes – maiores taxas de comportamento suicida e mais prejuízos funcionais [70,71]. Por ser um indicador precoce de auto desregulação com consequências para saúde mental a longo prazo, alguns pesquisadores apontam a irritabilidade como um bom marcador de risco [72], uma vez que intervenções adequadas podem reduzir a chance de crianças com irritabilidade desenvolverem diferentes formas de psicopatologia e desfechos negativos [73].

Estudos realizados em amostras populacionais e amostras clínicas de pacientes com TDAH mostram a associação entre irritabilidade e escore de risco poligênico para TDAH [74,75]. No entanto, os mecanismos subjacentes a irritabilidade em pacientes com TDAH não foram, até hoje, completamente elucidados. Déficits em memória operacional, controle inibitório, e flexibilidade cognitiva, comuns em pacientes com TDAH, podem contribuir para a ocorrência de irritabilidade. Contudo, não parecem explicar a ocorrência destes sintomas, uma vez que muitas das crianças com estas alterações não apresentam irritabilidade. Nesse contexto, alguns estudos sugerem que crianças com TDAH e irritabilidade podem representar um subgrupo de pacientes com correlatos fisiológicos, neurais e temperamentais distintos [65,76]. Além disso, os estudos indicam que algumas destas alterações não são específicas ao TDAH, e podem ser compartilhadas com outros quadros clínicos que também cursam com irritabilidade. Como mostram estudos realizados com amostras transdiagnósticas que mostram a associação entre irritabilidade e alterações no processamento de estímulos de ameaça ou de frustração [62,77]. Fatores ambientais como psicopatologia parental e práticas parentais inadequadas também podem contribuir para a ocorrência de irritabilidade [78]. Assim como, os sintomas de TDAH e a própria irritabilidade podem aumentar o estresse parental e evocar reações mais crítica e hostis [79].

Em relação ao tratamento, embora meta-análise realizada com estudos que incluíram crianças de 3-18 anos com TDAH tenha mostrado que treinamento parental

reduz problemas de conduta [10], e outra meta-análise realizada com estudos feitos com crianças de 2 e meio a 6 anos de idade, com diagnóstico ou sintomas de TDAH tenha mostrado efeito significativo do TPC sobre problemas de conduta relatados pelos pais não-cegos para a alocação de tratamento [55], nenhum desses estudos avaliou o efeito do tratamento especificamente sobre sintomas de irritabilidade.

Adicionalmente, para crianças em idade escolar com TDAH, análises *post-hoc* do estudo *Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA)* demonstraram que o uso de estimulantes foi superior à intervenção comportamental e que o tratamento combinado (i.e., medicação e intervenção comportamental) foi superior à intervenção comportamental e ao tratamento na comunidade em relação à redução de sintomas de irritabilidade[13]. Outra análise *post-hoc* de ensaio clínico realizado para avaliar o uso de lisdexanfetamina no tratamento de crianças escolares com TDAH também mostrou que o uso desta medicação reduz os sintomas de irritabilidade quando comparadas ao placebo [14]. No entanto, apesar dos achados obtidos em estudos com crianças escolares, faltam evidências sobre o efeito dos estimulantes na redução sintomas de irritabilidade em crianças pré-escolares com TDAH. Além disso, ensaios clínicos avaliando o uso de estimulantes para tratamento de crianças pré-escolares com TDAH indicam que labilidade emocional e irritabilidade são eventos adversos clinicamente significativos que ocorrem com maior frequência nesta população [15–17].

2.3.2 Avaliação de irritabilidade em crianças pré-escolares

Embora estudos já tenham demonstrado a associação entre irritabilidade na idade pré-escolar e diversos desfechos negativos ao longo da infância e adolescência [80,81], a avaliação desse sintoma em crianças pré-escolares ainda é bastante desafiadora. A apresentação da irritabilidade varia de acordo com o estágio de desenvolvimento da criança e, na idade pré-escolar, manifestações comportamentais de raiva ocorrem de forma frequente, como parte do desenvolvimento normal, exigindo grande conhecimento e habilidade clínica para diferenciar o normal do patológico. Além disso, os critérios estabelecidos pelas classificações diagnósticas tradicionais não levam em consideração aspectos desenvolvimentais e instrumentos destinados à avaliação de irritabilidade em crianças pré-escolares ainda são

escassos. Muitos dos instrumentos disponíveis avaliam construtos relacionados, como 'labilidade emocional' ou 'desregulação emocional' [64], ou se destinam a avaliação de crianças escolares e adolescentes [18].

Nesse contexto, um instrumento que se destaca é a *Multidimensional Assessment Profile of Disruptive Behavior* (MAP-DB). Esta é uma escala desenvolvida a partir de métodos estatísticos robustos e que, dentre cinco dimensões comportamentais (i.e., pouca preocupação com os outros, descontrole emocional, desobediência, agressividade e insensibilidade à punição), inclui a dimensão de 'descontrole emocional' (*Temper loss*) utilizada, na literatura, como uma medida de irritabilidade [21]. Um aspecto interessante da MAP-DB é que ela adota uma perspectiva dimensional e avalia a ocorrência um amplo espectro de comportamentos, incluindo comportamentos normativos e comportamentos atípicos para crianças pré-escolares [20,21,82]. No entanto, esta escala foi feita em inglês e somente foi traduzida e validada em Grego [83].

Atualmente, traduzido para o português do Brasil, há o *Child Behavior Checklist* (CBCL) 1.5-5, um inventário comportamental destinado à avaliação de crianças pré-escolares. Originalmente, o CBCL não inclui uma subescala para avaliação de irritabilidade. No entanto, itens derivados da subescala de oposição já foram utilizados para avaliação de irritabilidade em estudos anteriores [84–86]. Embora esta medida tenha se mostrado válida, ela é limitada do ponto de vista da caracterização dimensional deste sintoma. Há também a *Affective Reactivity Index* (ARI) [18], uma escala desenvolvida para avaliação de irritabilidade que se destaca por ser breve, ter boas propriedades psicométricas, já ter sido amplamente utilizada e por já ter sido traduzida em mais de 15 línguas, incluindo o português do Brasil [19]. Contudo, a ARI foi desenvolvida para avaliação de crianças escolares e adolescentes e até recentemente, não havia sido utilizada em amostras de crianças pré-escolares.

Portanto, instrumentos destinados a avaliação de irritabilidade, validados em amostras de crianças pré-escolares, e traduzidos para o português do Brasil, ainda se fazem necessários e poderão contribuir para o desenvolvimento de pesquisas sobre irritabilidade precoce no mundo e, particularmente, no Brasil.

3 OBJETIVOS

3.1 Objetivo geral

Avançar o conhecimento sobre o TDAH na idade pré-escolar, particularmente sobre os efeitos das diferentes modalidades de tratamento e sobre a avaliação de irritabilidade.

3.2 Objetivos específicos

3.2.1 Estudo 1 – Efficacy and safety of methylphenidate and behavioural parent training for children aged 3-5 years with attention-deficit hyperactivity disorder: a randomised, double-blind, placebo-controlled, and sham behavioural parent training-controlled trial (Mappa Study).

Objetivo primário: Avaliar a segurança e eficácia de metilfenidato e treinamento parental comportamental sobre a redução de sintomas de TDAH e melhora do funcionamento global no tratamento para crianças pré-escolares com TDAH por 8 semanas.

Objetivos secundários: Avaliar os efeitos de metilfenidato e treinamento parental comportamental sobre medida objetiva de desatenção e impulsividade, comportamentos disruptivos e irritabilidade, no tratamento para crianças pré-escolares com TDAH.

3.2.2 Estudo 2 - Efficacy of stimulants for preschool attention-deficit/hyperactivity disorder: A systematic review and meta-analysis.

Objetivo: revisar e sintetizar as evidências disponíveis na literatura sobre a eficácia e aceitabilidade do uso de estimulantes para tratamento de crianças pré-escolares com TDAH.

3.2.3 Estudo 3 - Validation of an irritability measure in preschoolers in school-based and clinical Brazilian samples.

Objetivo: Validar o uso da escala ARI (versão em português) em duas amostras brasileiras de crianças pré-escolares.

4 HIPÓTESES

4.1 Estudo 1 – *Efficacy and safety of methylphenidate and behavioural parent training for children aged 3-5 years with attention-deficit hyperactivity disorder: a randomised, double-blind, placebo-controlled, and sham behavioural parent training-controlled trial (Mappa Study).*

A hipótese a priori deste estudo foi que o uso de metilfenidato seria superior ao placebo na redução dos sintomas de TDAH e que o treinamento parental comportamental seria superior ao treinamento parental comportamental-*sham* na melhora da funcionalidade global de crianças pré-escolares com TDAH.

4.2 Estudo 2 - *Efficacy of stimulants for preschool attention-deficit/hyperactivity disorder: A systematic review and meta-analysis.*

A hipótese a priori deste estudo foi a de que o uso de estimulantes seria superior a placebo para reduzir sintomas de TDAH em crianças pré-escolares.

4.3 Estudo 3 - *Validation of an irritability measure in preschoolers in school-based and clinical Brazilian samples.*

A hipótese a priori deste estudo foi que a escala ARI apresentaria validade de construto e de conteúdo, consistência interna e confiabilidade adequadas nas duas amostras de crianças pré-escolares incluídas no estudo.

5 PRODUÇÃO CIENTÍFICA

5. 1 Artigo 1

Sugaya LS, Salum GA, de Sousa Gurgel W, de Morais EM, Del Prette G, Pilatti CD, Dalmaso BB, Leibenluft E, Rohde LA, Polanczyk GV. Efficacy and safety of methylphenidate and behavioural parent training for children aged 3-5 years with attention-deficit hyperactivity disorder: a randomised, double-blind, placebo-controlled, and sham behavioural parent training-controlled trial. *Lancet Child Adolesc Health*. 2022 Dec;6(12):845-856. doi: 10.1016/S2352-4642(22)00279-6.

5.2 Artigo 2

Sugaya LS, Farhat LC, Califano P, Polanczyk GV. Efficacy of stimulants for preschool attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *JCPP Advances*. 2023; e12146. doi: 10.1002/jcv2.12146

5.3 Artigo 3

Sugaya LS, Kircanski K, Stringaris A, Polanczyk GV, Leibenluft E. Validation of an irritability measure in preschoolers in school-based and clinical Brazilian samples. *Eur Child Adolesc Psychiatry*. 2022 Apr;31(4):577-587. doi: 10.1007/s00787-020-01701-6.

5.1 Artigo 1

Efficacy and safety of methylphenidate and behavioural parent training for children aged 3–5 years with attention-deficit hyperactivity disorder: A randomised, double-blind, placebo-controlled, and sham behavioural parent training-controlled trial.

Articles

Efficacy and safety of methylphenidate and behavioural parent training for children aged 3–5 years with attention-deficit hyperactivity disorder: a randomised, double-blind, placebo-controlled, and sham behavioural parent training-controlled trial

Luisa Shiguemi Sugaya, Giovanni Abrahão Salum, Wagner de Sousa Gurgel, Erika Mendonça de Morais, Giovana Del Prette, Caroline Drehmer Pilatti, Bianca Batista Dalmaso, Ellen Leibenluft, Luis Augusto Rohde, Guilherme Vanoni Polanczyk

Summary

Background There is insufficient evidence to support treatment recommendations for preschool children aged 3–5 years with attention-deficit hyperactivity disorder (ADHD). We aimed to investigate the efficacy and safety of methylphenidate and behavioural parent training in reducing the frequency and severity of symptoms and improving global functioning in preschool children with ADHD.

Methods We did an 8-week, randomised, double-blind, placebo-controlled and sham behavioural parent training-controlled clinical trial (the MAPPA Study) in children aged 3–5 years with moderate-to-severe ADHD. The trial was conducted at the Institute of Psychiatry, Hospital das Clinicas, University of São Paulo Medical School, São Paulo, Brazil. Participants were randomly assigned (1:1:1) to receive immediate-release methylphenidate plus educational intervention (sham behavioural parent training), placebo medication plus behavioural parent training, or placebo medication plus educational intervention. Randomisation was done by an independent research manager by use of a permuted block randomisation procedure. Parents, teachers, study staff, and evaluators remained masked to group allocation. Methylphenidate and placebo were titrated to a maximum dose of 1·25 mg/kg per day administered orally twice daily, and behavioural parent training and the educational intervention were delivered weekly through 90 min sessions with both the child and parent, conducted by two psychologists or learning therapists. The primary outcomes were parents' and teachers' composite scores of the Swanson, Nolan, and Pelham-IV scale (SNAP-IV-P/T), the Clinical Global Impressions Severity (CGI-S) scale, and the Children's Global Assessment Scale (CGAS). This trial is registered with ClinicalTrials.gov, NCT02807870, and is now complete. All participants were invited to participate in an open observational follow-up, which is ongoing.

Findings Between Aug 21, 2016, and Oct 21, 2019, 153 children were randomly assigned to receive methylphenidate plus the educational intervention (n=51), placebo plus behavioural parent training (n=51), or placebo plus the educational intervention (n=51). Nine (6%) children discontinued treatment. All participants were included in the intention-to-treat analysis. Children in the methylphenidate plus educational intervention group showed greater reductions in the SNAP-IV-P/T (endpoint mean difference –3·93 [95% CI –7·14 to –0·73], p=0·049; effect size –0·55 [95% CI –0·99 to –0·10]) and CGI-S scores (endpoint mean difference –0·49 [–0·82 to –0·17], p=0·0088; effect size –0·70 [–1·16 to –0·24]) and a greater increase in CGAS scores (endpoint mean difference 5·25 [95% CI 2·09 to 8·40], p=0·0036; effect size 0·80 [95% CI 0·32 to 1·28]) than children in the placebo plus educational intervention group. Children in the placebo plus behavioural parent training group did not have significantly different SNAP-IV-P/T scores (endpoint mean difference –3·18 [95% CI –6·38 to 0·02], p=0·077; effect size –0·44 [95% CI –0·89 to 0·003]) or CGI-S scores (endpoint mean difference –0·35 [–0·68 to –0·03], p=0·052; effect size –0·50 [–0·96 to –0·04]) compared to children in the placebo plus educational intervention group, but they had a greater increase in CGAS scores compared to the placebo plus educational intervention group (endpoint mean difference 3·69 [0·53 to 6·85], p=0·033; effect size 0·56 [0·08 to 1·04]). Children in the methylphenidate plus educational intervention versus placebo plus behavioural parent training group did not have statistically or clinically significant differences in primary outcomes. Children in the methylphenidate plus educational intervention group had more mild adverse events than the other two groups, and there were no between-group differences for moderate or severe adverse events.

Interpretation Methylphenidate was effective in reducing ADHD symptoms and improving functionality, and behavioural parent training was effective in improving functionality for preschool children with ADHD after 8 weeks of treatment.

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that typically emerges in early childhood[1] and affects approximately 2% of preschool children (ie, those aged 3–5 years).[2] Preschool ADHD increases the risk of morbidity[3] and mortality,[4] necessitating effective intervention.[5]

Clinical guidelines recommend behavioural parent training as a first-line intervention followed by stimulants if substantial impairment or symptoms remain.[6] Behavioural parent training was developed to treat disruptive behaviours[7] and is oriented around functional problems and the impairment arising from ADHD. There is evidence that this intervention improves parenting and other outcomes related to ADHD,[8] but there is uncertainty about its effect on core ADHD symptoms because these are commonly reported in randomised controlled trials by parents who are usually unmasked to treatment allocation.[9,10]

Clinicians prescribe medications such as stimulants, alfa-agonists, and antipsychotics more frequently than behavioural parent training for preschool children,[11,12] despite limited evidence of the efficacy of these agents[5] and concerns about their safety and overuse.[13,14] National estimates in the USA suggest that 76% of children aged 2–5 years in clinical care for ADHD receive medications.[12] However, many children can go untreated because there is limited access to behavioural parent training globally. In the USA, only about 55% of preschool children or parents of preschool children with ADHD receive psychological treatment.[12] Thus, randomised controlled trials that evaluate the efficacy and safety of both stimulants and behavioural parent training as first-line treatment options and that include full masking of both treatments are considered a top priority in the field.

We aimed to investigate the efficacy and safety of methylphenidate and behavioural parent training in reducing the frequency and severity of ADHD symptoms and improving global functioning in preschool children. Our a-priori hypothesis was that methylphenidate would be superior to placebo in reducing core symptoms and that behavioural parent

Research in context

Evidence before this study

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that typically emerges in early childhood. There is insufficient evidence to support treatment recommendations for preschool children aged 3–5 years with ADHD. Behavioural parent training produces improvements in measures of parenting, but a meta-analysis showed that its effect on reduction of ADHD symptoms is probably only significant in an unmasked setting. Nevertheless, few studies have been conducted with masked parents and teachers. Randomised controlled trials have documented the safety and efficacy of stimulants in preschool children, with a lower magnitude of effect sizes and more adverse events than reported for school-age children. Currently available network meta-analyses of medications have excluded preschool children. No randomised controlled trial has, to the best of our knowledge, tested the comparative efficacy and safety of methylphenidate and behavioural parent training by ensuring masked outcome assessment and with adequate control groups. Before the MAPPA study commenced in August, 2016, we searched ClinicalTrials.gov, EMBASE, and PubMed for randomised controlled trials assessing the efficacy of stimulant medications and behavioural parent training for participants younger than 6 years with ADHD. We also searched reference lists of systematic reviews on the subject. No relevant studies were identified.

Added value of this study

We report, to the best of our knowledge, the results of the first randomised controlled trial designed to evaluate the efficacy and safety of stimulants and behavioural parent training as first-line treatment options for preschool children with ADHD. Our study had multiple strengths, including sham behavioural parent training to control for improvements due to non-specific aspects of psychotherapy and ensure masking of parents and independent evaluators; a relatively large sample size; outcomes informed by parents, teachers, clinicians, and objective measures; detailed documentation of side-effects; and low attrition. In this 8-week randomised controlled trial of 153 preschool children, methylphenidate reduced the frequency and severity of ADHD symptoms and improved global functioning. Behavioural parent training improved global functioning. Methylphenidate produced more mild adverse events than other interventions.

Implications of all the available evidence

Methylphenidate was well tolerated and effective in reducing the frequency and severity of ADHD symptoms and improving global functioning. Behavioural parent training was not superior to placebo plus educational intervention (sham behavioural parent training) in reducing the frequency and severity of ADHD symptoms but did improve global functioning. Participants showed adherence to both methylphenidate and behavioural parent training. These results should be beneficial to clinicians making treatment recommendations, which will take into consideration symptom severity, presence of disruptive behaviours or irritability, or both, functional impairment, parental dysfunction, family preference, accessibility of interventions, and other specific patient and family characteristics. Preschool children with ADHD should not be left untreated until they reach school age or the impairment becomes severe, and they should receive treatments supported by the best available evidence.

training would be superior to sham behavioural parent training in improving functionality.

Methods

Study design and participants

This 8-week, randomised, double-blind, placebo-controlled and sham behavioural parent training-controlled clinical trial was conducted at the Institute of Psychiatry, Hospital das Clínicas, University of São Paulo Medical School, São Paulo, Brazil, and approved by its human research ethics committee. Written informed consent was provided by the parent or primary caregiver of each participant. The study protocol is available in the appendix (pp 37–89).

Eligible participants were children aged 3–5 years (47–71 months) recruited by referral from other public mental health centres and from online media who met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for ADHD,[15] including the presence of symptoms across different contexts and significant functional impairment. Clinical assessment and diagnosis were done by six child and adolescent psychiatrists (including the coauthors LSS, WdSG, and EMdM) who were experienced in preschool mental health and trained and supervised by the senior investigator (GVP). Diagnosis was based on the semi-structured interview Kiddie Schedule for Affective Disorders and Schizophrenia Lifetime Version (K-SADS-PL)[16] following the Research Diagnostic Criteria-Preschool Age (RDC-PA),[17] an adaptation for this age group (appendix pp 81–87). Inter-rater reliability across all six clinicians for all diagnoses was excellent (k>0·78).

Inclusion criteria included moderate or severe symptoms, defined as parent ratings of 32 or greater on the Swanson, Nolan, and Pelham-IV scale (SNAP-IV),[18] a scale commonly used in paediatric clinical trials of ADHD, and registration of the child in a school or daycare centre. Children were not eligible if they had an IQ less than 70; affective, psychotic, or autism spectrum disorders; used psychotropic medications during the previous 30 days; a major clinical condition (eg, unstable epilepsy or cardiovascular disease); a history of neurological disorder or head trauma with loss of consciousness; or if their parent or caretaker were unable to understand the study objectives and instructions.

The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)[19] was administered by a neuropsychologist. Other measures were collected by trained research assistants to characterise the sample and to investigate secondary outcomes. Details are provided in the study protocol in the appendix (pp 51–62).

Randomisation and masking

Eligible participants were randomly assigned (1:1:1) into three groups: methylphenidate plus educational intervention (sham behavioural parent training); placebo medication plus behavioural parent training; and placebo medication plus educational intervention. Randomisation was conducted by an independent research manager through the website www.randomization.com by use of a permuted block randomisation procedure with equal allocation and five blocks of n=30. Parents, teachers, study staff, and evaluators remained masked to group allocation. Masking was ensured by rigorous procedures. A full description of the procedures is given in the appendix (pp 3, 63–64).

Procedures

In the methylphenidate group, immediate-release methylphenidate was administered orally, twice a day, for 8 weeks. A child and adolescent psychiatrist masked to treatment group assessed the children bi-weekly (and whenever parents requested), and titration was done weekly following a flexible dosing regimen. Recommended doses during the first 4 weeks of treatment were 0·3 mg/kg per day in the first week, 0·5 mg/kg per day in the second week, and 0·7 mg/kg per day in the third and fourth weeks. From week 5 onwards, doses could be titrated to 1·0 mg/kg per day and then up to 1·25 mg/kg per day if there was room for improvement and no limiting adverse effects. The dosage could be decreased at any time because of adverse effects. Residual pills were returned and counted weekly.

See Online for appendix

Placebo was cornflour only, encapsulated in capsules identical to the methylphenidate capsules in colour, size, and weight. Placebo titration was done following the same procedure.

Behavioural parent training was done according to the Helping the Noncompliant Child[20] protocol (appendix pp 108–251). Helping the Noncompliant Child has been compared to the New Forest Parenting Package, another behavioural parent training protocol for the treatment of preschool children with ADHD, and both were shown to be effective according to parent ratings.[21] The Helping the Noncompliant Child protocol is based on social learning and behaviour modification principles and is designed to teach parents how to manage children's behaviour, improve parent–child relationships, and parental competencies. It was designed to treat disruptive behaviours and is oriented towards functional problems; it is not directed specifically towards ADHD symptoms. The programme consists of eight weekly individual sessions of 90 min each, with the child and parent together, conducted by two psychologists specialised in behavioural therapy. Therapists were trained by a certified trainer of the Helping the Noncompliant Child protocol during two annual workshops and were continuously supervised by a local senior behavioural therapist (GDP).

The educational intervention was a sham behavioural parent training intervention to control for attention from therapists to parents and children, which both groups received, and other non-specific aspects of behavioural

parent training and to ensure complete masking to treatment allocation.

The educational intervention protocol was developed by the MAPPA investigators and focuses on typical child development (appendix pp 252–91). It was designed to inform parents about child development, has no active technique included, and does not address any aspect of ADHD. The educational intervention followed the same structure as the behavioural parent training programme (ie, eight weekly individual sessions of 90 min each with both child and parent). Sessions were conducted by two psychologists or learning therapists who had no training in behavioural therapy following the educational intervention protocol and were continuously supervised by a senior psychologist.

	Methylphenidate plus educational intervention (n=51)	Placebo plus behavioural parent training (n=51)	Placebo plus educational intervention (n=51)	Total (n=153)
Child demographics				
Age, months	60·06 (7·93)	60·82 (7·94)	60·47 (7·03)	60·45 (7·60)
Sex				
Male	44 (86%)	43 (84%)	41 (80%)	128 (84%)
Female	7 (14%)	8 (16%)	10 (20%)	25 (16%)
Mean IQ score*	89·24 (11·10)	90·06 (11·08)	91·12 (11·44)	90·14 (11·16)
ADHD presentation				
Inattention	4 (8%)	4 (8%)	3 (6%)	11 (7%)
Hyperactivity or impulsivity	12 (24%)	12 (24%)	10 (20%)	34 (22%)
Combined	35 (69%)	35 (69%)	38 (75%)	108 (71%)
Number of comorbidities				
0	15 (29%)	18 (35%)	23 (45%)	56 (37%)
1	20 (39%)	17 (33%)	18 (35%)	55 (36%)
2	9 (18%)	9 (18%)	8 (16%)	26 (17%)
≥3	7 (14%)	7 (14%)	2 (4%)	16 (10%)
Comorbidities				
Oppositional defiant disorder	26 (51%)	23 (45%)	17 (33%)	66 (43%)
Conduct disorder	9 (18%)	4 (8%)	3 (6%)	16 (10%)
Enuresis or encopresis	8 (16%)	6 (12%)	5 (10%)	19 (12%)
Simple phobia	9 (18%)	12 (24%)	10 (20%)	31 (20%)
Other anxiety disorders	6 (12%)	6 (12%)	3 (6%)	15 (10%)
Other disorders	4 (8%)	5 (10%)	2 (4%)	11 (7%)
Baseline clinical scores				
SNAP-IV-P				
Total†	38·49 (9·13)	37·92 (7·95)	37·78 (6·94)	38·07 (8·01)
Inattention‡	18·16 (4·49)	17·53 (4·61)	17·73 (3·95)	17·80 (4·34)
Hyperactivity or impulsivity‡	20·33 (5·32)	20·39 (4·83)	20·06 (3·81)	20·26 (4·67)
SNAP-IV-T§				
Total†	35·90 (10·21)	33·86 (12·13)	33·86 (10·87)	34·53 (11·07)
Inattention‡	17·29 (6·52)	16·08 (6·67)	15·50 (5·59)	16·28 (6·28)
Hyperactivity impulsivity‡	18·61 (6·90)	17·78 (7·41)	18·36 (6·77)	18·25 (6·99)
SNAP-IV-P/T				
Total†	37·38 (7·75)	35·90 (7·24)	35·92 (6·60)	36·40 (7·20)
Inattention‡	17·78 (4·32)	16·76 (4·02)	16·67 (3·88)	17·07 (4·08)
Hyperactivity or impulsivity‡	19·60 (4·89)	19·14 (4·65)	19·25 (3·79)	19·33 (4·44)
CGI-S¶	4·82 (0·68)	4·67 (0·77)	4·65 (0·66)	4·71 (0·70)
CGAS‖	48·82 (7·12)	49·47 (6·26)	48·51 (6·39)	48·93 (6·57)

(Table 1 continues on next page)

Outcomes

Children were assessed at baseline and weeks 4 and 8. The first primary outcome was ADHD symptoms measured by the SNAP-IV scale,[18] which was rated by a masked independent evaluator based on parental interview (SNAP-IV-P) and completed independently by teachers (SNAP-IV-T) who were also masked to treatment conditions. For analyses, we computed average scores across parent and teacher SNAP-IV (SNAP-IV-P/T) ratings (appendix p 4). There was no a priori hypothesis of different effects on dimensions. The second primary outcome was clinical severity measured by the Clinical Global Impressions Severity (CGI-S) scale,[22] rated by masked independent evaluators on the basis of parents' interviews. The third primary outcome was the child's global functioning measured by the Clinical Global Assessment Scale (CGAS)[23] and assessed at baseline and week 8 by the masked psychiatrist who was following the participant throughout the study, thus providing cross-informant validation of outcomes.

Secondary outcomes were an objective cognitive measure, the Conners Kiddie Continuous Performance Test (KCPT-2);[24] and questionnaires used to assess irritability and disruptive behaviours: the Affective Reactivity Index (ARI)[25] and the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB).[26] These clinically relevant symptoms are frequently associated with ADHD and have been shown to respond to behavioural parent training. All secondary outcomes were assessed at baseline and week 8. A detailed description of the secondary outcomes is given in the appendix (p 5).

Adverse events were investigated through the Barkley's Side-Effect Rating Scale[27] (SERS) and measures of bodyweight, height, and BMI assessed weekly; clinical assessments with a register of parental spontaneous report and physical examination conducted bi-weekly; and laboratory exams and electrocardiograms done at baseline and week 8. For a detailed description of these assessments see the appendix (p 6).

Statistical analysis

The sample size was calculated for a 0·05 one-sided type I error and 80% power to detect treatment differences in the prespecified primary efficacy endpoint comparisons: methylphenidate plus educational intervention versus placebo plus educational intervention and placebo plus behavioural parent training versus placebo plus educational intervention. Based on the

published literature,[28] we predicted a mean difference between treatment groups of 5·94 SNAP-IV units and an SD of 10·62, yielding an effect size of 0·56 (Cohen's d). The calculated sample size was 41 participants in each group. To account for a predicted 20% dropout rate, we aimed to enrol 150 participants (50 per group).

All participants were included in the intention-to-treat analysis according to randomised treatment assignment. For primary and secondary outcome analyses, we used random intercepts mixed-effects models for continuous outcomes. This is an extension of a general linear model frequently used in randomised controlled trials that is appropriate for clustered and repeated-measures data. The model takes into account the hierarchical structure of the data to deal with within-participant and between-participant variance including both fixed and random effects. It uses maximum likelihood estimation to handle missing data assuming missing at random. Independent models included, as fixed effects, time (three levels: baseline, week 4, and week 8), group (three levels: methylphenidate plus educational intervention, placebo plus behavioural parent training, and placebo plus educational intervention), time-by-group interaction, and comorbidity (two levels: present and absent); and, as random effects, participants (153 levels) and year of data collection (three levels: 1, 2, and 3 years). In these models, time was treated as a categorical variable. For adverse events analyses, time was treated as a continuous variable and only participants (153 levels) were entered as a random variable. Time-by-group interactions for the primary and secondary outcomes and adverse events were explored by use of least squares means, adjusting for multiple comparisons by the Benjamini and Hochberg method. Post-hoc pairwise comparisons included estimated differences from baseline to week 8 in each group and between-group differences in estimated week 8 scores. The statistical analysis plan is shown in the appendix (pp 90–107).

All analyses were done in R (version 3.5.2) with the package lme4 and lmerTest for conducting mixed-effects models. Estimated marginal means were calculated with the packages effects and emmeans. Statistical analyses were done by an independent investigator (GAS) masked to the treatment group variable.

Minor changes to the study protocol were made during the study period and are detailed in the appendix (pp 7, 88–89); in brief, in the first protocol amendment (Jan 16, 2013), no participant was assessed; in the second (April 27, 2015), a pilot study with 12 participants was conducted and no participants were enrolled for this trial; in the third (March 14, 2016), no participants were enrolled; in the fourth (May 8, 2016), 38 participants were enrolled; and in the fifth (Aug 6, 2017), 115 participants were enrolled. These changes are not expected to have any effect on study outcomes.

There were two protocol deviations. First, 47 (31%) children did not present with a score of 32 or greater on parent-reported SNAP-IV at the eligibility interview. Second, for 28 (18%) participants, different teachers completed the baseline and outcome assessments. The sensitivity analysis showed no effect of these deviations on the primary outcomes, as described in the appendix (pp 11–16).

The trial is registered with ClinicalTrials.gov, NCT02807870.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, and data interpretation, the writing of the report or the decision to submit the paper for publication.

Results

Between Aug 21, 2016, and Oct 21, 2019, 153 children were enrolled and randomly assigned into the three treatment groups (n=51 per group). The mean age was 60·45 months (SD 7·60); clinical characteristics of the participants are summarised in table 1. Most (84%) participants were boys, 71% had a combined ADHD presentation, and 63% had at least one comorbid disorder; 81% of parents had a high school or college

	Methylphenidate plus educational intervention (n=51)	Placebo plus behavioural parent training (n=51)	Placebo plus educational intervention (n=51)	Total (n=153)
(Continued from previous page)				
Parent demographics				
Mean IQ score**	101·96 (11·26)	106·34 (11·33)	101·31 (11·77)	103·18 (11·60)
Education (head of household)				
Did not complete middle school	7 (14%)	2 (4%)	3 (6%)	12 (8%)
Completed middle school	8 (16%)	3 (6%)	6 (12%)	17 (11%)
Completed high school	21 (41%)	25 (49%)	21 (41%)	67 (44%)
Completed college or graduation	15 (29%)	21 (41%)	21 (41%)	57 (37%)
Brazilian criteria socioeconomic status††	25·60 (7·40)	30·37 (7·86)	30·25 (9·05)	28·76 (8·38)

Data are mean (SD) or n (%). ADHD=attention deficit and hyperactivity disorder. CGAS=Children's Global Assessment Scale. CGI-S=Clinical Global Impression–Severity scale. SNAP-IV-P=Swanson, Nolan, and Pelham-IV scale completed by parents. SNAP-IV-T=Swanson, Nolan, and Pelham-IV scale completed by teachers. SNAP-IV-P/T=average scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV scale. *51 participants in the methylphenidate plus educational intervention group; 50 participants in the placebo plus behavioural parenting training group; and 51 participants in the placebo plus educational intervention group. †SNAP total scores range from 0 to 54, with higher scores indicating more severe symptoms. ‡SNAP inattention scores and SNAP hyperactivity-impulsivity scores range from 0 to 27, with higher scores indicating more severe symptoms. §49 participants in the methylphenidate plus educational intervention group; 50 participants in the placebo plus behavioural parenting training group; and 50 participants in the placebo plus educational intervention group. ¶CGI-S scores range from 1 (normal, not at all ill) to 7 (extremely ill). ||CGAS scores range from 1 to 100, with higher scores indicating better global functioning. **51 participants in the methylphenidate plus educational intervention group; 50 participants in the placebo plus behavioural parenting training group; 51 participants in the placebo plus educational intervention group. ††A measure developed by the Brazilian Association of Research Companies based on the possession of durable goods, the employment of a housekeeper, and the level of education attained by the head of the household. Scores range from 0 to 100. According to estimates from the 2020 National Household Sample Survey, scores of 25–28 represent a monthly income of R$3194, and scores of 29–37 reflect a monthly income of R$5721.

Table 1: **Baseline demographic and clinical characteristics**

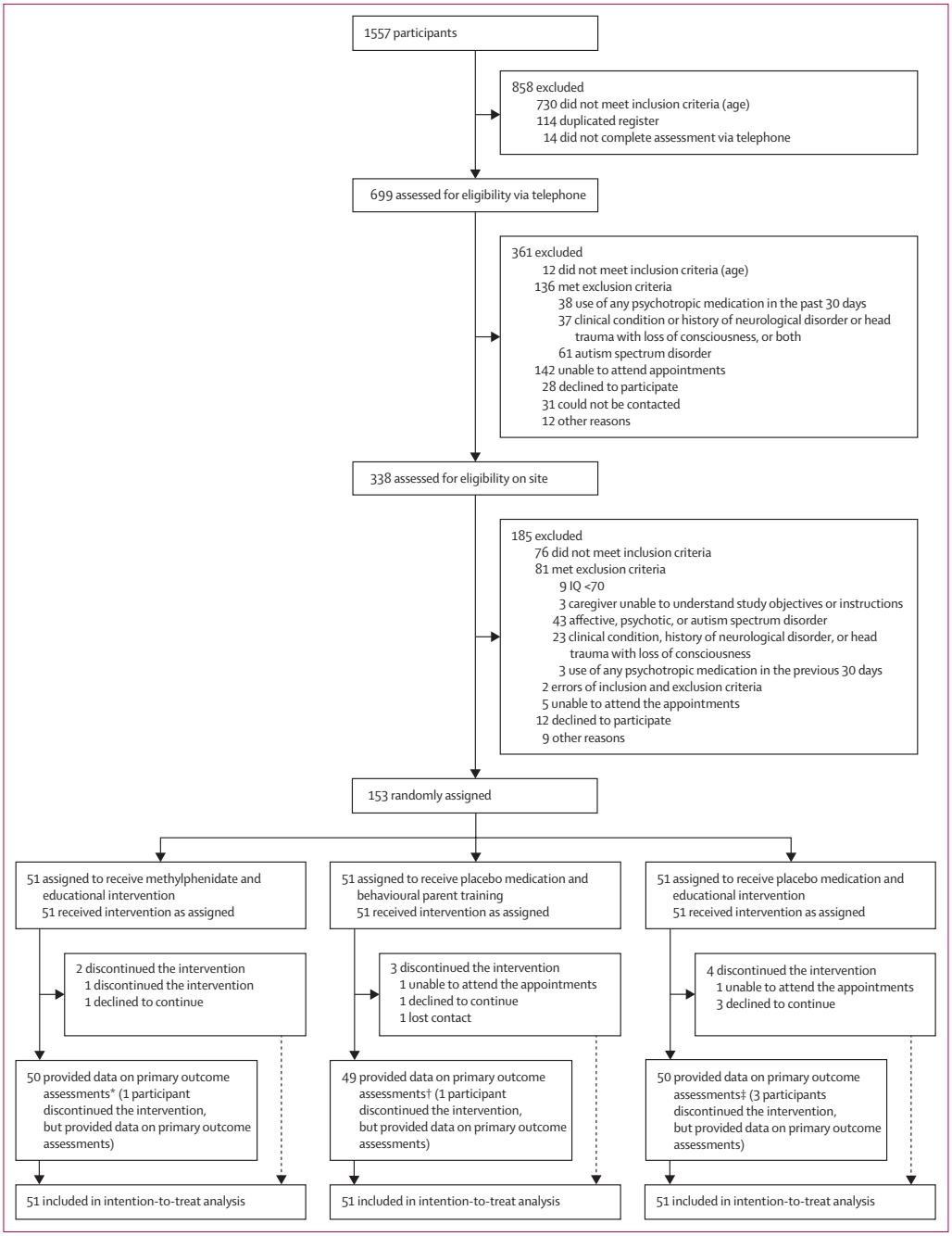

Figure 1: **Trial profile**
*Three participants with missing teachers' outcome assessments; 11 participants with one teacher outcome assessment. †Two participants with missing teachers' outcome assessments; 14 participants with one teacher outcome assessment. ‡One participant with one parent and clinician outcome assessment; five participants with missing teachers' outcome assessments; 13 participants with one teacher outcome assessment completed.

degree. Nine (6%) participants discontinued treatment, none because of adverse events (figure 1). Missing data on outcome assessment are presented in the appendix (p 17). 142 (93%) of 153 participants completed at least seven of eight possible behavioural parent training or educational intervention sessions, and 134 (88%) of 153 received the maximum dose (1·25 mg/kg per day) of methylphenidate or placebo, representing a mean absolute dose per day of 26·99 mg (SD 6·15; appendix pp 18–19).

In primary outcome analyses for ADHD symptoms, time-by-group interactions were detected for SNAP-IV-P/T scores and there were differences at week 8 only between the methylphenidate plus educational intervention and placebo plus educational intervention groups (mean difference –3·93 [95% CI –7·14 to –0·73], p=0·049, effect size –0·55 [95% CI –0·99 to –0·10]; table 2; figure 2). Scores for each dimension of symptoms are presented in the appendix (pp 9–10). For severity of the disorder and global functioning, time-by-group interactions were detected for CGI-S and CGAS scores (table 2; figure 2). For the CGI-S score, there was a difference at week 8 between the methylphenidate plus educational intervention and placebo plus educational intervention groups (mean difference –0·49, [95% CI –0·82 to –0·17], p=0·0088, effect size –0·70 [95% CI –1·16 to –0·24]). For the CGAS, there were differences at week 8 between the methylphenidate plus educational intervention and placebo plus educational intervention groups (mean difference 5·25 [95% CI 2·09 to 8·40], p=0·0036, effect size 0·80 [95% CI 0·32 to 1·28]) and between the placebo plus behavioural parent training and placebo plus educational intervention groups (mean difference 3·69 [95% CI 0·53 to 6·85], p=0·033, effect size 0·56 [95% CI 0·08 to 1·04]). There were no differences between the methylphenidate plus educational intervention and placebo plus behavioural parent training groups.

In sensitivity analyses described in the appendix (pp 20–22), we investigated SNAP-IV-P and SNAP-IV-T ratings separately. There was a time-by-group interaction for SNAP-IV-P total score and differences at week 8 between the methylphenidate plus educational intervention and placebo plus educational intervention groups (mean difference –5·87 [95% CI –9·34 to –2·40], p=0·0029, effect size –0·73 [95% CI –1·17 to –0·30]) and between the placebo plus behavioural parent training and placebo plus educational intervention groups (mean difference –4·21 [95% CI –7·68 to –0·75], p=0·026, effect size –0·53 [95% CI –0·78 to –0·08]). There were no significant time-by-group interactions for SNAP-IV-T total scores.

In the secondary outcome analyses, for the KCPT-2, time-by-group interactions were observed for detectability, hit reaction time SD (HRT-SD), and commissions, which are indicators of inattentiveness. For detectability and HRT-SD, pairwise comparisons showed a significant effect of methylphenidate plus educational intervention compared to both placebo plus behavioural parent training (detectability: mean difference –5·36 [95% CI –8·65 to –2·08], p=0·0046, effect size –0·92 [95% CI –1·48 to –0·36]; HRT SD: mean difference –9·04 [–15·51 to –2·58], p=0·016, effect size –0·74 [–1·27 to –0·21]); and placebo plus educational intervention (detectability: mean difference –4·83 [–8·22 to –1·45], p=0·0081, effect size –0·83 [–1·41 to –0·25]; HRT SD: mean difference –8·67 [–15·33 to –2·02], p=0·016, effect size –0·71 [–1·25 to –0·17]). No significant between-group differences at week 8 were found for commissions (appendix pp 23–25). For the ARI score, a time-by-group interaction and endpoint differences at week 8 were

	SNAP-IV-P/T*	CGI-S scale†	CGAS‡
Difference between baseline and week 8			
Methylphenidate plus educational intervention			
Baseline mean (SE)	37·07 (1·65)	4·77 (0·14)	48·98 (1·18)
Week 8 mean (SE)	28·16 (1·66)	3·85 (0·14)	57·57 (1·19)
Mean difference (95% CI)§	8·90 (6·91 to 10·90)	0·92 (0·68 to 1·16)	–8·59 (–11·16 to –6·03)
Placebo plus behavioural parent training			
Baseline mean (SE)	35·74 (1·65)	4·63 (0·14)	49·57 (1·17)
Week 8 mean (SE)	28·92 (1·66)	3·99 (0·14)	56·02 (1·20)
Mean difference (95% CI)§	6·82 (4·81 to 8·83)	0·64 (0·40 to 0·89)	–6·44 (–9·02 to –3·86)
Placebo plus educational intervention			
Baseline mean (SE)	36·08 (1·66)	4·63 (0·14)	48·57 (1·18)
Week 8 mean (SE)	32·10 (1·67)	4·34 (0·14)	52·33 (1·22)
Mean difference (95% CI)§	3·98 (1·97 to 5·99)	0·29 (0·05 to 0·53)	–3·76 (–6·36 to –1·16)
Time-by-group interaction, p value¶	0·0057	0·0099	0·035
Results of pairwise comparison			
Methylphenidate plus educational intervention *vs* placebo plus behavioural parent training			
Mean difference (95% CI)‖	–0·75 (–3·94 to 2·43)	–0·14 (–0·47 to 0·18)	1·56 (–1·57 to 4·68)
p value	0·64	0·39	0·33
Effect size (95% CI)**	–0·10 (–0·55 to 0·34)	–0·20 (–0·66 to 0·26)	0·24 (–0·24 to 0·71)
Methylphenidate plus educational intervention *vs* placebo plus educational intervention			
Mean difference (95% CI)‖	–3·93 (–7·14 to –0·73)	–0·49 (–0·82 to –0·17)	5·25 (2·09 to 8·40)
p value	0·049	0·0088	0·0036
Effect size (95% CI)**	–0·55 (–0·99 to –0·10)	–0·70 (–1·16 to –0·24)	0·80 (0·32 to 1·28)
Placebo plus behavioural parent training *vs* placebo plus educational intervention			
Mean difference (95% CI)‖	–3·18 (–6·38 to 0·02)	–0·35 (–0·68 to –0·03)	3·69 (0·53 to 6·85)
p value	0·077	0·052	0·033
Effect size (95% CI)**	–0·44 (–0·89 to 0·003)	–0·50 to –0·96 to –0·04)	0·56 (0·08 to 1·04)

CGAS=Children's Global Assessment Scale. CGI-S=Clinical Global Impression–Severity scale. SNAP-IV-P/T=average scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV scale. All participants were included in the intention-to-treat analysis. Descriptive statistics reflect the estimated marginal means from mixed-effect models analyses. Time-by-group interaction and pairwise comparison results are also based on estimated data from the mixed-effect models analyses. *SNAP-IV-P/T score ranges from 0 to 54, with higher scores indicating more severe symptoms. †CGI-S scores range from 1 (normal, not at all ill) to 7 (extremely ill). ‡CGAS scores range from 1 to 100, with higher scores indicating better global functioning. §Mean difference between baseline and week 8 post-treatment. ¶p value for time-by-group interaction term. ‖Mean difference between groups in estimated endpoint scores. **Effect sizes were calculated with standardised mean difference (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at baseline (SD pooled SNAP-IV-P/T total=7·20; SD pooled CGAS=6·57; SD pooled CGI-S=0·70).

Table 2: **Summary of primary outcome analyses**

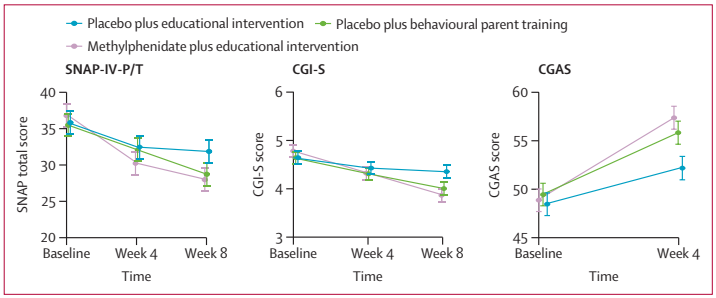

Figure 2: **Changes in primary outcomes by treatment group and time**
Estimated marginal means from mixed-effects model analyses are shown by week and treatment group. Bars indicate standard errors (SE). CGAS=Children's Global Assessment Scale. CGI-S=Clinical Global Impression–Severity scale. SNAP-IV-P/T=average scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV scale.

observed between the placebo plus behavioural parent training and placebo plus educational intervention groups (mean difference –1·60 [95% CI –2·81 to –0·39], p=0·029, effect size –0·50 [95% CI –0·88 to –0·12]; appendix pp 26–27). For the MAP-DB score, a time-by-group interaction was detected only for the Temper Loss dimension, here used as an irritability measure. Significant differences at week 8 were observed between the methylphenidate plus educational intervention and placebo plus behavioural parent training groups (mean difference 8·85 [95% CI 1·57 to 16·13], p=0·026, effect size 0·43 [95% CI 0·08 to 0·77]) and between the placebo plus behavioural parent training and placebo plus educational intervention groups (mean difference –14·08 [–21·46 to –6·70], p=0·0006, effect size –0·68 [–1·03 to –0·32]; appendix pp 26–27). Although the time-by-group interaction for the MAP-DB non-compliance dimension was not significant, there was a difference at week 8 between placebo plus behavioural parent training and placebo plus educational intervention groups (mean difference –12·24 [95% CI –20·95 to –3·53], p=0·0018, effect size –0·51 [95% CI –0·87 to –0·15]; appendix pp 26–27).

According to parental spontaneous reporting, 794 adverse events occurred in 134 (91%) of 148 children (table 3). The number of mild adverse events reported in the methylphenidate plus educational intervention group was higher than in the other two groups; there was no significant difference between groups in the number of moderate or severe adverse events. 99 (67%) of 148 children had only mild adverse events and 33 (22%) of 148 had moderate adverse events. Two children had severe adverse events not related to the study interventions. One child in the methylphenidate plus educational intervention group was admitted to hospital because of an asthma attack and one child in the placebo plus behavioural parent training group was admitted to hospital because of H1N1 influenza infection. There were no between-group differences in the number of children with adverse events (table 3). Decreased appetite and insomnia occurred more frequently in the methylphenidate plus educational intervention group than in the other two groups, and increased appetite occurred more frequently in placebo plus behavioural parent training and placebo plus educational intervention groups than in the methylphenidate plus educational intervention group (appendix pp 28–33).

On the SERS, total score and decreased appetite score showed significant time-by-group interactions. Post-hoc pairwise comparisons for the SERS total score showed no between-group differences, and children in the methylphenidate plus educational intervention group had greater appetite reduction than those in the placebo plus behavioural parent training group (mean difference 1·99 [95% CI 1·15 to 2·82], p<0·0001, effect size 0·94 [95% CI 0·54 to 1·33]) and those in the placebo plus educational intervention group (mean difference 1·58 [0·73 to 2·43], p<0·0001, effect size 0·75 [0·35 to 1·15]; appendix pp 34–35). There were time-by-group interactions for bodyweight and BMI. Children in the methylphenidate plus educational intervention group had bodyweight and BMI reductions from baseline to week 8 but there were no endpoint differences between treatment groups (appendix pp 34–35). No abnormalities requiring clinical intervention were detected in ECG and laboratory tests (table 3). Four children (one in the methylphenidate plus educational intervention group and three in the placebo plus educational intervention group) presented with a heart rate greater than 120 bpm at two visits, and four children (two in the methylphenidate plus educational intervention group and two in the placebo plus behavioural parent training group) presented with high blood pressure at three visits (table 3).

Discussion

This randomised controlled trial assessed the efficacy and safety of methylphenidate and behavioural parent training during 8 weeks of treatment in 153 preschool children with ADHD. Results show that methylphenidate led to a moderate reduction in the frequency and severity of ADHD symptoms and associated improvement in global functioning in comparison with placebo plus educational intervention. Behavioural parent training was not superior to placebo plus educational intervention in reducing ADHD symptoms, but produced improvement in global functioning. Most participants received their treatment as intended, adverse events were mild, and only nine (6%) discontinued treatment. The significance of this study stems from its methodology, including control for expectancy effects of medication and psychotherapy, assurance of parental masking, detailed documentation of side-effects, and the low dropout rate. These aspects of the study design allowed us to generate high-quality evidence to inform treatment recommendations for preschool children with ADHD.

The effect size of methylphenidate in reducing ADHD symptoms in preschool children was –0·55, a moderate effect size consistent with findings from the PATS Study[28] and lower than the effect size of –0·78 reported in school-age children.[29] There was no clear evidence of the efficacy of behavioural parent training in reducing symptoms, although the direction of the effect on primary outcomes consistently favoured behavioural parent training compared to placebo plus educational intervention. In the sensitivity analysis, using parent-reported scores only, methylphenidate and behavioural parent training were both superior to placebo plus educational intervention, with effect sizes of –0·73 with methylphenidate and –0·53 with behavioural parent training.

Because our methods were designed to ensure parental masking, report bias was likely to be minimal. Teachers did not detect significant effects of methylphenidate or behavioural parent training compared with placebo plus educational intervention, which is contrary to the literature.[28] This might have occurred because treatment effects were not generalisable to the school setting.

	Methylphenidate plus educational intervention	Placebo plus behavioural parent training	Placebo plus educational intervention	Total	p value*
Adverse events reported by parents during clinical evaluations					
Number of adverse events					
Mild adverse event	332	235	227	794	<0·0001†
Moderate adverse event	15	22	14	51	0·23
Severe adverse event	1	1	0	2	0·77
Number of children with adverse events					
No adverse event	4/51 (8%)	6/49 (12%)	4/48 (8%)	14/148 (10%)	0·68
Only mild adverse events	36/51 (71%)	28/49 (57%)	35/48 (73%)	99/148 (67%)	..
At least one moderate adverse event	10/51 (20%)	14/49 (29%)	9/48 (19%)	33/148 (22%)	..
At least one severe adverse event	1/51 (2%)	1/49 (2%)	0/48 (0%)	2/148 (1%)	..
SERS					
SERS total score at week 8‡§	19·11 (14·89)	14·91 (16·65)	16·62 (15·43)	16·87 (15·67)	0·43
Number of children with severe adverse events (SERS score ≥7 at least once during treatment)					
Stomachaches	1/51 (2%)	3/50 (6%)	0/49 (0%)	4/150 (3%)	0·22
Dizziness	0/51 (0%)	0/50 (0%)	0/49 (0%)	0/150 (0%)	..
Headaches	3/51 (6%)	4/50 (8%)	3/49 (6%)	10/150 (7%)	0·92
Drowsiness	1/51 (2%)	4/50 (8%)	3/49 (6%)	8/150 (5%)	0·36
Motor tics	4/51 (8%)	6/50 (12%)	3/49 (6%)	13/150 (9%)	0·59
Nightmares	5/51 (10%)	7/50 (14%)	4/49 (8%)	16/150 (11%)	0·62
Insomnia or restless sleeping	17/51 (33%)	11/50 (22%)	9/49 (18%)	37/150 (25%)	0·19
Decreased appetite	13/51 (26%)	10/50 (20%)	3/49 (6%)	26/150 (17%)	0·032¶
Anxiousness	18/51 (35%)	16/50 (32%)	16/49 (33%)	50/150 (33%)	0·93
Bites fingernails	11/51 (22%)	14/50 (28%)	9/49 (18%)	34/150 (23%)	0·51
Irritability	22/51 (43%)	14/50 (28%)	19/49 (39%)	55/150 (37%)	0·27
Prone to crying	16/51 (31%)	17/50 (34%)	10/49 (20%)	43/150 (29%)	0·29
Depressed, sad, unhappy	0/51 (0%)	1/50 (2%)	0/49 (0%)	1/150 (1%)	0·66
Unusually happy	5/51 (10%)	6/50 (12%)	3/49 (6%)	14/150 (9%)	0·65
Uninterested in others	5/51 (10%)	1/50 (2%)	2/49 (4%)	8/150 (5%)	0·25
Talking little with others	7/51 (14%)	1/50 (2%)	2/49 (4%)	10/150 (7%)	0·07
Daydreaming	4/51 (8%)	6/50 (12%)	1/49 (2%)	11/150 (7%)	0·17
Physical examination					
Bodyweight changes from baseline to week 8 (kg)‖	–0·14 (1·05)	0·46 (0·99)	0·53 (0·64)	0·29 (0·94)	0·0012**
BMI percentile at week 8					
<3 (underweight)	0/42 (0%)	0/40 (0%)	0/43 (0%)	0/125 (0%)	..
3–84 (healthy)	32/42 (76%)	24/40 (60%)	24/43 (56%)	80/125 (64%)	0·12
85–97 (risk of overweight)	2/42 (5%)	7/40 (18%)	11/43 (26%)	20/125 (16%)	0·031††
>97 (overweight)	8/42 (19%)	9/40 (23%)	8/43 (19%)	25/125 (20%)	0·89
Heart rate >120 bpm at 2 visits	1/51 (2%)	0/50 (0%)	3/48 (6%)	4/149 (3%)	0·12
Blood pressure >95th percentile at 3 visits	2/51 (4%)	2/50 (4%)	0/48 (0%)	4/149 (3%)	0·55

(Table 3 continues on next page)

	Methylphenidate plus educational intervention	Placebo plus behavioural parent training	Placebo plus educational intervention	Total	p value*
(Continued from previous page)					
Exams					
ECG at week 8					
Heart rate (bpm) >124 (female) or >123 (male)	1/48 (2%)	0/47 (0%)	0/47 (0%)	1/142 (1%)	>0·99
PR interval (ms) <99 (female) or <98 (male)	2/48 (4%)	0/47 (0%)	0/47 (0%)	2/142 (1%)	0·33
PR interval (ms) >153 (female) or >152 (male)	0/48 (0%)	6/47 (13%)	2/47 (4%)	8/142 (6%)	0·028‡‡
QRS duration (ms) >88 (female) or >92 (male)	2/48 (4%)	2/47 (4%)	1/47 (2%)	5/142 (4%)	1·0
QTc interval (ms) >442 (female) or >448 (male)	3/48 (8%)	3/47 (9%)	6/47 (18%)	12/142 (12%)	0·41
Increased septal electrical forces	0/48 (0%)	0/47 (0%)	1/47 (2%)	1/142 (0·7%)	0·66
Short PR interval	1/48 (2%)	0/47 (0%)	0/47 (0%)	1/142 (0·7%)	1·0
Early transition	3/48 (6%)	0/47 (0%)	1/47 (2%)	4/142 (3%)	0·32
Early repolarisation	2/48 (4%)	1/47 (2%)	0/47 (0%)	3/142 (2%)	0·77
Incomplete right bundle branch block	0/48 (0%)	1/47 (2%)	0/47 (0%)	1/142 (0·7%)	0·66
End conduction delay	1/48 (2%)	3/47 (6%)	1/47 (2%)	5/142 (4%)	0·53
Laboratory tests at week 8					
ALT ≥41 U/L	0/48 (0%)	3/47 (6%)	0/47 (0%)	3/142 (2%)	0·11
AST ≥37 U/L	7/48 (15%)	4/47 (9%)	5/47 (11%)	16/142 (11%)	0·61
ALP ≥269 U/L	10/48 (21%)	13/47 (28%)	7/47 (15%)	30/142 (21%)	0·32
Bilirubin total >1·0 mg/dL	0/48 (0%)	1/47 (2%)	3/47 (6%)	4/142 (3%)	0·32
Haemoglobin <11·7 g/dL	5/48 (11%)	1/47 (2%)	1/47 (2%)	7/142 (5%)	0·22
Leukocytes <5500 per µL	3/48 (7%)	5/47 (11%)	1/47 (2%)	9/142 (6%)	0·25
Leukocytes >15 500 per µL	2/48 (4%)	0/47 (0%)	2/47 (4%)	4/142 (3%)	0·47
Platelet count >450 × 10^3 per µL	8/48 (17%)	5/47 (11%)	3/47 (6%)	16/142 (11%)	0·26

Data are mean (SD) or n/N (%). SERS=Barkley's Side-Effect Rating Scale. ECG=electrocardiogram. ALP=alkaline phosphatase. ALT=alanine aminotransferase. AST=aspartate aminotransferase. Adverse events were classified as mild if they did not require any further action. Adverse events were classified as moderate if they required medical evaluation or interventions (eg, dosage adjustment or the use of an over-the-counter medication). Adverse events were classified as severe if they represented a serious medical threat (eg, seizure). *For categorical variables, we used the χ^2 test of homogeneity, and multiple z-tests of two proportions with Bonferroni correction, for pairwise comparisons. Fisher's exact test was used if more than 20% of cells have expected counts below 5. For continuous variables one-way ANOVA and the Scheffe post-hoc test were used. †Pairwise comparisons: methylphenidate plus educational intervention group had more mild adverse events than did the placebo plus behavioural parent training and placebo plus educational intervention groups. ‡SERS total scores range from 0 to 103, with higher scores indicating more severe adverse events. §Assessed in 46 participants in the methylphenidate plus educational intervention group, 47 participants in the placebo plus behavioural parent training group, and 45 participants in the placebo plus educational intervention group. ¶Pairwise comparisons: methylphenidate plus educational intervention group had a greater number of children with decreased appetite rated as severe (SERS score ≥7) than did placebo plus educational intervention group. ||Assessed in 40 participants in the methylphenidate plus educational intervention group, 38 participants in the placebo plus behavioural parent training group, and 43 participants in the placebo plus educational intervention group. **Pairwise comparisons: methylphenidate plus educational intervention group had a smaller change in bodyweight than did the placebo plus behavioural parent training and placebo plus educational intervention groups. ††Pairwise comparisons: methylphenidate plus educational intervention group had a smaller number of children with risk of overweight (BMI percentile 85–97) than did the placebo plus educational intervention group. ‡‡Pairwise comparisons: methylphenidate plus educational intervention group had a smaller number of children with PR interval >153 (female) or >152 (male) than did the placebo plus behavioural parent training group.

Table 3: **Summary of adverse events**

Additionally, cultural aspects and characteristics of the education system in Brazil (eg, higher tolerance to hyperactivity and resistance from teachers in relation to psychiatric diagnosis; preschools offer child-led play-based activities for half the day) could hinder identification of ADHD symptoms in this age group, as baseline scores informed by teachers were lower than those informed by parents. Additionally, because the research team had less control over completion of SNAP-IV by teachers, further measurement error might have occurred, in contrast to clinician interviews with parents.

Secondary outcomes indicated specific effects for each of the active treatments. Compared to both placebo plus behavioural parent training and placebo plus educational intervention, methylphenidate was associated with greater improvements in cognitive measures of attention. However, behavioural parent training was associated with improvement in irritability compared to methylphenidate and placebo plus educational intervention. This finding is in line with theory and evidence showing that behavioural parent training is efficacious in the management of disruptive behaviours and functional problems during daily routines. It is relevant to note that the slightly elevated rates of comorbid oppositional defiant disorder and conduct disorder in the placebo plus behavioural parent training group compared with the placebo plus educational intervention group might have increased the chances of behavioural parent training having an improvement in children with these comorbidities. Reduction in irritability or non-compliance,

or both, might have contributed to improvement in global functioning.

Methylphenidate was associated with more mild adverse events than the other two groups, and appetite reduction with methylphenidate was identified consistently across different strategies of assessment. Although children treated with methylphenidate had a reduction in bodyweight over time, children in the other groups presented with bodyweight gain, as expected. This effect, together with possible effects on height, should be monitored over time and balanced against symptom improvement. There were two severe adverse effects, neither related to the study interventions. No ECG or laboratory abnormalities were associated with methylphenidate use and, unlike previous studies,[28] there was no dropout due to adverse events. Gradual and flexible titration and frequent clinical assessments might have contributed to higher safety and tolerability of treatment. Doses were optimised as planned, reaching absolute doses comparable to previous studies[28] but with a twice-daily regimen. This regimen could restrict the duration of effect of the medication but could also minimise adverse effects in preschool children, especially effects related to appetite reduction at dinnertime and insomnia at early bedtime that is typical in this age group.

Our study has some limitations. First, the findings were restricted to 8 weeks, and different results might have been seen with long-term treatment. The evidence generated here does not address questions such as the continued efficacy or cumulative adverse impact of either methylphenidate or behavioural parent training over longer time periods. Second, it was not possible to have complete teacher reports for all participants, and measurement error might have influenced their reports. Third, as in other randomised controlled trials done in university hospitals, results were obtained under optimal conditions and might not be generalisable to all settings because of staff characteristics (eg, experience with preschool children, intensive training, and continuous supervision) or characteristics of the population included in the study. Our sample is similar to the PATS Study[28] sample in terms of age, sex distribution, severity of symptoms and functional impairment, presentation of symptoms, and number of comorbid disorders. However, our sample had lower IQ scores (mean IQ score of 90 *vs* 97 in PATS) and parents or caregivers were less educated (81% were high school graduates in our sample *vs* 96% in PATS). In our study, parents were highly motivated and attrition was low. Fourth, the sample size calculation was based on reduction of ADHD symptoms, and analysis with different outcomes might be underpowered. Fifth, we did not include a fourth group combining methylphenidate and behavioural parent training; this might have implications for clinical practice, since the combined treatment might produce different effects to treatment with a single intervention. Finally, the study was done at a single centre, which might limit generalisability to other settings. Nevertheless, the study was done at a hospital that serves a diverse population of more than 20 million people. Moreover, a single-centre study guarantees homogeneity in data collection and treatment.

Strengths of our study include a sham-behavioural parent training group that controlled for non-specific effects of psychotherapy and ensured masking of parents, clinicians, and independent evaluators; a relatively large sample size; outcomes informed by parents, teachers, clinicians, and objective measures; delivery of interventions as planned; and low attrition in all treatment groups. All primary and secondary outcomes were defined a priori and are reported here. Investigation of moderators and mediators of treatments effects will be reported separately at a later date.

Methylphenidate was well tolerated and effective in reducing the frequency and severity of ADHD symptoms and improving global functioning. Behavioural parent training was not superior to placebo plus educational intervention in reducing the frequency and severity of ADHD symptoms but did improve global functioning. Participants showed adherence to both methylphenidate and behavioural parent training. These results should be considered by clinicians making treatment recommendations, which will take into consideration symptom severity, presence of disruptive behaviours or irritability, or both, functional impairment, parental dysfunction, family preference, accessibility of interventions, and other specific patient and family characteristics. Preschool children with ADHD should not be left untreated until they reach school age or their impairment becomes severe and they should receive treatments supported by the best available evidence.

MAPPA investigators

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Contributors

GVP and LAR conceived and designed the trial and GVP was the principal investigator. LSS, LAR, and GVP contributed to the protocol and design of the study. LSS and GAS accessed and verified the data, and GAS did the statistical analysis. LSS, GAS, EL, LAR, and GVP contributed to the preparation of the report. All other authors

contributed to the implementation of the study and data collection. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

GVP has, in the past 3 years, been a consultant, member of advisory board, or speaker, or a combination of the above, for Takeda, Medice, Aché, Novo Nordisk, and Abbott; and has received royalties from Editora Manole. LAR has received grant or research support from, served as a consultant to, and served on the speakers' bureau of Aché, Bial, Medice, Novartis/ Sandoz, Pfizer/Upjohn, and Shire/Takeda in the past 3 years. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by LAR have received unrestricted educational and research support from the following pharmaceutical companies in the past 3 years: Novartis/Sandoz and Shire/Takeda. LAR has received authorship royalties from Oxford University Press and ArtMed. All other authors declare no competing interests.

Data sharing

Anonymised participant data will be made available when the trial is published, upon requests directed via email to the corresponding author. Proposals will be reviewed and approved by the investigators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement. All data will be made available for a minimum of 5 years from publication.

Acknowledgments

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5.1.1 Artigo 1: material suplementar

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sugaya LS, Salum GA, de Sousa Gurgel W, et al. Efficacy and safety of methylphenidate and behavioural parent training for children aged 3–5 years with attention-deficit hyperactivity disorder: a randomised, double-blind, placebo-controlled, and sham behavioural parent training-controlled trial. *Lancet Child Adolesc Health* 2022; published online Oct 25. https://doi.org/10.1016/S2352-4642(22)00279-6.

Supplementary Appendix

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Randomization and blinding

The randomization scheme was generated by an independent research manager with experience in the execution of clinical trials and no involvement in this trial using a permuted block randomization procedure with equal allocation and 5 blocks with N=30 ⟨http://www.randomization.com⟩. Three additional participants that had initiated the pre-trial assessment before the inclusion of the 150th participant were considered eligible and were randomized. For their inclusion, an identical randomization scheme was generated, except that the block size was 3.

Parents, teachers, child and adolescent psychiatrists that conducted child's initial assessment and clinical evaluations during the trial, research assistants, and independent evaluators remained fully blinded. Only the study research coordinator and therapists were unblinded to psychological treatment but they remained blinded to medication treatment. Only the study pharmacist was unblinded to medication treatment, but remained blinded to psychological treatment. Also, the independent investigator (GAS) who conducted data analysis remained blinded to study groups until the analyses were completed. For details, see the study protocol (pp 62-63).

Parents and teachers' ratings integration

Informant's discrepancies on behavioral reports have long been described[1]. These discrepancies may reflect different factors, including behavior variability across settings, differential contextual demands, behavior presentation (e.g., internalizing and externalizing behaviors), and informants' and child' characteristics. Evidence suggests that child evaluations should consider these discrepancies rather than dismiss them as measurement errors [2–4].

ADHD diagnostic criteria require that symptoms must be present in two or more settings, and consideration of parents' and teachers' ratings increase ADHD diagnosis validity [5,6]. Nevertheless, there is no consensus about the best evidence-based method for integrating data from multiple informants. Averaging parents' and teachers' ratings may be an optimal approach [5,7]. In this direction, Martel et al. (2015) compared the average approach to two commonly used approaches: the ''OR" algorithm (in which a symptom is present if endorsed by either informant), and the "AND" algorithm (in which a symptom is present if endorsed by both informants). They found that the average approach had stronger correlations with ADHD latent factors and outperformed both the "OR" and "AND" algorithms in the prediction of ADHD diagnosis [5]. More recently, Martel et al. (2021) found that the average approach outperformed the "OR" and "AND" algorithms in predictions of concurrent and longitudinal impairment ratings [7]. The average approach has already been used in randomized clinical trials evaluating the treatment of children with ADHD [8,9]. Other approaches, such as multitrait-multimethod matrix, confirmatory factor analysis, and item response theory are promising, but they are complex and may have more limited clinical utility [4].

Thus, for primary outcome analysis, a composite score for each ADHD symptom was computed by averaging parents' (SNAP-IV-P) and teachers' (SNAP-IV-T) ratings. When there were only parent's or teacher's ratings, missing values were treated as zero. Average scores were summed to compute the SNAP-IV-P/T inattention, SNAP-IV-P/T hyperactivity/impulsivity, and SNAP-IV-P/T total scores. In addition, for sensitivity analyses, we analyzed SNAP-IV-P and SNAP-IV-T ratings separately.

Secondary Outcomes

K-CPT-2

Conners Kiddie Continuous Performance Test (K-CPT-2) [10] was used to assess attention-related problems at baseline and at the end of treatment. In the K-CPT-2, poor Detectability (d'), a high percentage of Omissions and Commissions, slow Hit reaction Time (HRT), and high levels of inconsistency in response speed (Hit Reaction Time Standard Deviation [HRT-SD] and Variability) were indicators of inattentiveness. Faster than normal Hit Reaction Time (HRT), in addition to a higher-than-average rate of Commissions and/or Perseverations, were indicators of impulsivity.

Irritability and disruptive behavior

Irritability and disruptive behaviors, in general, are major clinical complaints frequently associated with ADHD. Therefore, we investigated these symptoms at baseline and at the end of treatment with the Affective Reactivity Index (ARI) [11], a measure of irritability; and the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB) [12], a multidimensional questionnaire that assesses five dimensions of disruptive behaviors (i.e., temper loss, aggression, noncompliance, low concern to others, and insensitivity to punishment). Here, the MAPDB temper loss dimension was also used as a measure of irritability.

Adverse Events

Adverse events were investigated using three strategies. First, all adverse events reported spontaneously by parents were documented by the child's psychiatrist. Based on parent report, an independent clinician rated each adverse event 'mild' if it did not require any further action; 'moderate' if it required medical evaluation or intervention (e.g., dosage adjustment or the use of an over-the-counter medication); or 'severe' if it represented a serious medical threat (e.g., seizure).

Second, at each weekly visit, parents completed the Barkley's Side-Effect Rating Scale (SERS) [13], a 9-point Likert scale, ranging from 0 (absent) to 9 (severe). Adverse events were classified as 'present' if ratings ≥1, and as 'severe' if ratings ≥7[10]. Total adverse event scores were calculated as the sum of all items. Third, electrocardiogram (ECG), complete blood count, and liver enzymes were collected at baseline and after 8 weeks of treatment. Child's weight, height, and body mass index (BMI) were measured weekly; and physical examinations, including heart rate and blood pressure, were conducted by a clinician biweekly. Heart rate above 120 bpm at 2 visits and high blood pressure (i.e., blood pressure ≥ 95th percentile) at 3 visits were also registered as adverse events.

Protocol amendments and deviations

Protocol amendments

Five versions of the protocol were used during the study period. Under the first version (version 1.0, dated January 16, 2013), no participant was assessed. Under the second version (version 1.1, dated April 27, 2015), a pilot study with 12 participants was conducted and no participants were enrolled for this trial. Under the third version (version 1.2, dated March 14, 2016), no participants were enrolled. Under the fourth version (version 1.3, dated May 8, 2016), 38 participants were enrolled. Under the fifth version (version 1.4, dated August 6, 2017), 115 participants were enrolled. Changes included in each of these amendments are detailed in the study protocol (pp 87-88). These changes were minimal and not expected to have any effect on study outcomes.

Protocol deviations

There were two deviations of the protocol. First, 47 (30.7%) children (MPH+EI=19, PLB+BPT=15, PLB+EI=13) did not present a score ≥ 32 or greater on parent SNAP-IV at the eligibility interview and were deemed eligible for full clinical assessment and inclusion because, by parent report at the interview, they had moderate to severe symptoms with functional impairment and were clinically symptomatic as reported by teachers. Second, for 28 (18.3%) participants (MPH+EI=5, PLB+BPT=12, PLB+EI=11), different teachers completed the baseline and the outcome assessments.

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Table S1. Number of children per group and previous interventions before (lifetime) entering the MAPPA Study.

	MPH+EI (n=51)	PBO+BPT (n=51)	PBO+EI (n=51)	Total (n=153)
Pharmacological				
Methylphenidate IR	0	1 (2%)	1 (2%)	2 (1%)
Methylphenidate LA	0	0	1 (2%)	1 (0.7%)
Clonidine	0	2 (4%)	0	2 (1%)
Antipsychotics				
Risperidone	3 (6%)	4 (8%)	0	7 (5%)
Periciazine	0	0	1 (2%)	1 (0.7%)
Mood Stabilizer				
Valproic acid	0	1 (2%)	0	1 (0.7%)
Carbamazepine	0	2 (4%)	0	2 (1%)
Antidepressant				
Fluoxetine	0	1 (2%)	0	1 (0.7%)
Imipramine	0	3 (6%)	0	3 (2%)
Other				
Melatonin	0	0	1 (2%)	1 (0.7%)
Herbal medicine / homeopathy	3 (6%)	7 (14%)	5 (10%)	15 (10%)
Non-pharmacological				
Psychotherapy [a]	11(22%)	10 (20%)	10 (20%)	31 (20%)

[a] Number of participants that had previous psychotherapy, conducted with any technique, during at least 8 sessions of at least 30min/session. The data was obtained through parents' reports.

Table S2. Treatment effect on SNAP-IV-P/T Inattention and SNAP-IV-P/T hyperactivity/impulsivity. [a]

	MPH+EI			PLB+BPT			PLB+EI			Time x Group Inter. P[c]	Results of Pairwise Comparison								
											MPH+EI vs. PLB+BPT			MPH+EI vs. PLB+EI			PLB+BPT vs.PLB+EI		
	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)		Mean Diff. [d] (CI)	p	ES [e] (CI)	Mean Diff. [d] (CI)	p	ES [e] (CI)	Mean Diff. [d] (CI)	p	ES [e] (CI)
SNAP-IV-P/T Inattention [f,g]	17·63 (0·90)	13·20 (0·90)	4·43 (3·35, 5·50)	16·67 (0·90)	13·22 (0·90)	3·45 (2·37, 4·54)	16·72 (0·90)	14·82 (0·91)	1·90 (0·82, 2·99)	0·018	-0·02 (-1·72, 1·68)	0·98	-0.004 (-0·42, 0·41)	-1·62 (-3·33, 0·09)	0·10	-0·40 (-0·82, 0·02)	-1·60 (-3·31, 0·11)	0·10	-0·39 (-0·81, 0·03)
SNAP-IV-P/T Hyperactivity, Impulsivity [f,g]	19·45 (0·84)	14·97 (0·85)	4·48 (3·33, 5·62)	19·07 (0·84)	15·70 (0·85)	3·37 (2·21, 4·52)	19·35 (0·85)	17·27 (0·85)	2·08 (0·93, 3·23)	0·015	-0·73 (-2·64, 1·18)	0·45	-0·16 (-0·59, 0·27)	-2·30 (-4·22, -0·37)	0·058	-0·52 (-0·95, -0·08)	-1·57 (-3·49, 0·35)	0·16	-0·35, -0·78, 0·08)

Abbreviations: CI, 95% confidence interval; ES, effect size; Mean Diff, mean difference; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SE, standard error; SNAP-IV-P/T, average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV

[a] All participants were included in an intent-to-treat analysis. Descriptive statistics reflect the estimated marginal means from Mixed Effect Models (MEM) analyses. Treatment by time interaction and pairwise comparison results are also based on estimated data from the MEM analyses.

[b] Mean difference between baseline and posttreatment

[c] P value for treatment by time interaction term.

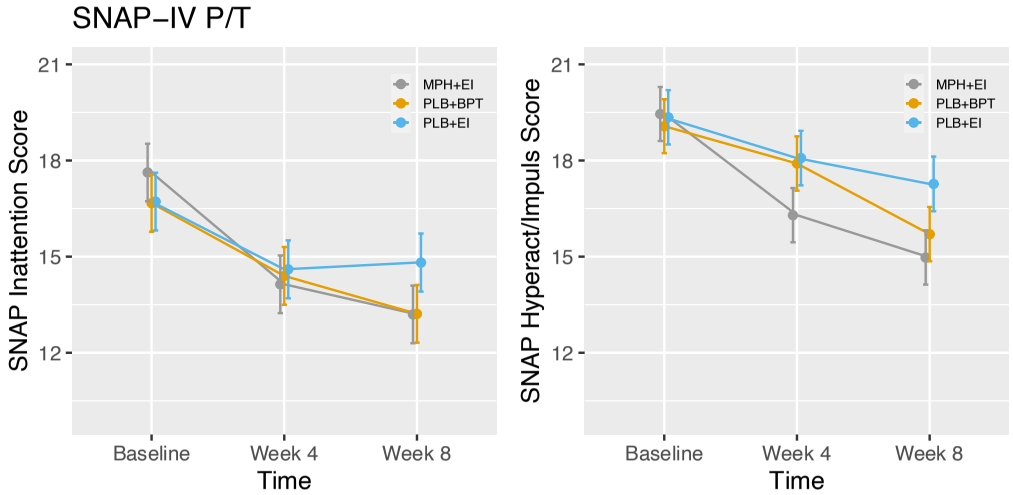
[d] Mean difference between groups in estimated endpoint scores.

[e] Effect sizes were calculated using standardized mean difference (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at the baseline (SD pooled SNAP-IV-P/T Inattention: 4.08, SD pooled SNAP-IV-P/T hyperactivity/Impulsivity: 4.44)

[f] SNAP-IV-P/T was computed as the average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV.

[g] SNAP Inattention scores and SNAP Hyperactivity-impulsivity scores range from 0 to 27, with higher scores indicating more severe symptoms.

Figure S1. Changes in SNAP-IV-P/T Inattention and SNAP-IV-P/T Hyperactivity/Impulsivity by Treatment Group and Time



Abbreviations: MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SNAP-IV-P/T, average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV.
Estimated marginal means from Mixed Effect Models (MEM) analyses are displayed by week and treatment group. Bars indicate standard errors (SE).

Sensitivity analyses including only participants with a score of 32 or greater on parent SNAP-IV at the eligibility interview (N=106)

Due to a protocol deviation, 47 (30.7%) children did not present a score of ≥ 32 on parent SNAP-IV at the eligibility interview. Thus, for sensitivity analyses, we repeated the primary outcomes analyses including only participants with SNAP ≥ 32 at the eligibility interview (n=106, n=32 MPH+EI; n=36 PLB+BPT; n=38 PLB+EI). Time by group interactions were detected for SNAP-IV-P/T total and inattention scores. No significant endpoint difference between groups were found (Table S3). Figure S2 shows changes in primary outcomes by treatment group and time.

Table S3. Sensitivity analyses: primary outcome analyses including only participants with a score of 32 or greater on parent SNAP-IV at the eligibility interview (n=106) [a, b]

	MPH+EI			PLB+BPT			PLB+EI			Time x Group Inter. P[d]	Results of Pairwise Comparison								
											MPH+EI vs. PLB+BPT			MPH+EI vs. PLB+EI			PLB+BPT vs.PLB+EI		
	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [c] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [c] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [c] (CI)		Mean Diff. [e] (CI)	p	ES[f](CI)	Mean Diff. [e] (CI)	p	ES[f](CI)	Mean Diff. [e] (CI)	p	ES[f](CI)
SNAP-IV-P/T [g]																			
Total [h]	39·15 (1·87)	30·09 (1·88)	9·05 (6·47, 11·64)	37·19 (1·81)	29·45 (1·83)	7·74 (5·28, 10·20)	36·99 (1·81)	33·25 (1·82)	3·74 (1·38, 6·11)	0·028	0·65 (-3·21, 4·50)	0·74	0·09 (-0·46, 0·64)	-3·15 (-7·04, 0·73)	0·17	-0·45 (-1·00, 0·10)	-3·80 (-7·54, -0.05)	0·14	-0·54 (-1·08, -0·007)
Inattention [i]	17·97 (1·12)	13·44 (1.13)	4·53 (3·10, 5·96)	16·96 (1·09)	13·08 (1·10)	3·88 (2·52, 5·24)	17·17 (1·09)	15·55 (1·10)	1·62 (-0·31, 2·93)	0·035	0·36 (-1·78, 2·50)	0·74	0·08 (-0·42, 0·59)	-2·11 (-4·27, 0·05)	0·083	-0·49 (-1·00, 0·01)	-2·47 (-4·55, -0·39)	0·060	-0·58 (-1·07, -0·09)
Hyperactivity, Impulsivity [i]	21·19 (0·87)	16·66 (0·87)	4·53 (3·10, 5·95)	20·23 (0·83)	16·36 (0·84)	3·86 (2·50, 5·22)	19·82 (0·82)	17·70 (0·83)	2·12 (0·82, 3·42)	0·092	0·24 (-1·84, 2·43)	0·79	0·08 (-0·51, 0·67)	-1·03 (-3·19, 1·12)	0·52	-0·29 (-0·88, 0·31)	-1·33 (-3·41, 0·75)	0·52	-0·37 (-0·94, 0·21)
CGI-S [j]	4·94 (0·15)	4·04 (0·15)	0·90 (0·59, 1·22)	4·78 (0·14)	3·98 (0·15)	0·80 (0·50, 1·11)	4·73 (0·14)	4·45 (0·14)	0·29 (-0·005, 0·58)	0·05	0·60 (-0·33, 0·45)	0·77	0·07 (-0·39, 0·54)	-0·41 (-0·80, -0·02)	0·06	0·48 (-0·95, -0·02)	-0·47 (-0·85, -0·09)	0·05	-0·55 (-1·00, 0·10)
CGAS [k]	47·91 (1·37)	57·44 (1·39)	-9·53 (-12·68, -6·38)	47·99 (1·28)	54·13 (1·32)	-6·14 (-9·13, -3·14)	48·16 (1·27)	52·57 (1·30)	-4·41 (-7·32, -1·49)	0·06	3·32 (-0·45, 7·08)	0·13	0·53 (-0·07, 1·12)	-4·87 (1·08, 8·67)	0·04	0·77 (0·17, 1·38)	1·56 (-2·12, 5·23)	0·40	0·25 (-0·33, 0·83)

Abbreviations: CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression – Severity scale; CI, 95% confidence interval; ES, effect size; Mean Diff, mean difference; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SE, standard error; SNAP-IV, Swanson, Nolan, and Pelham-IV; SNAP-IV-P/T, average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV.

[a] n=32 MPH+EI; n=36 PLB+BPT; n=38 PLB+EI

[b] Descriptive statistics reflect the estimated marginal means and proportions from Mixed Effect Models (MEM) analyses. Treatment by time interaction and pairwise comparison results are also based on estimated data from the MEM analyses.

[c] Mean difference between baseline and posttreatment

[d] P value for treatment by time interaction term.

[e] Mean difference between groups in estimated endpoint scores

[f] Effect sizes were calculated as standardized mean differences (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at baseline (SD pooled SNAP-IV-P/T Total = 6.99; SD pooled SNAP-IV-P/T Inattention = 4.25, SD pooled SNAP-IV-P/T Hyperactivity/Impulsivity = 3.62; SD pooled CGI-S = 0.62, SD pooled CGAS = 6.30).

[g] SNAP-IV-P/T was computed as average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV.

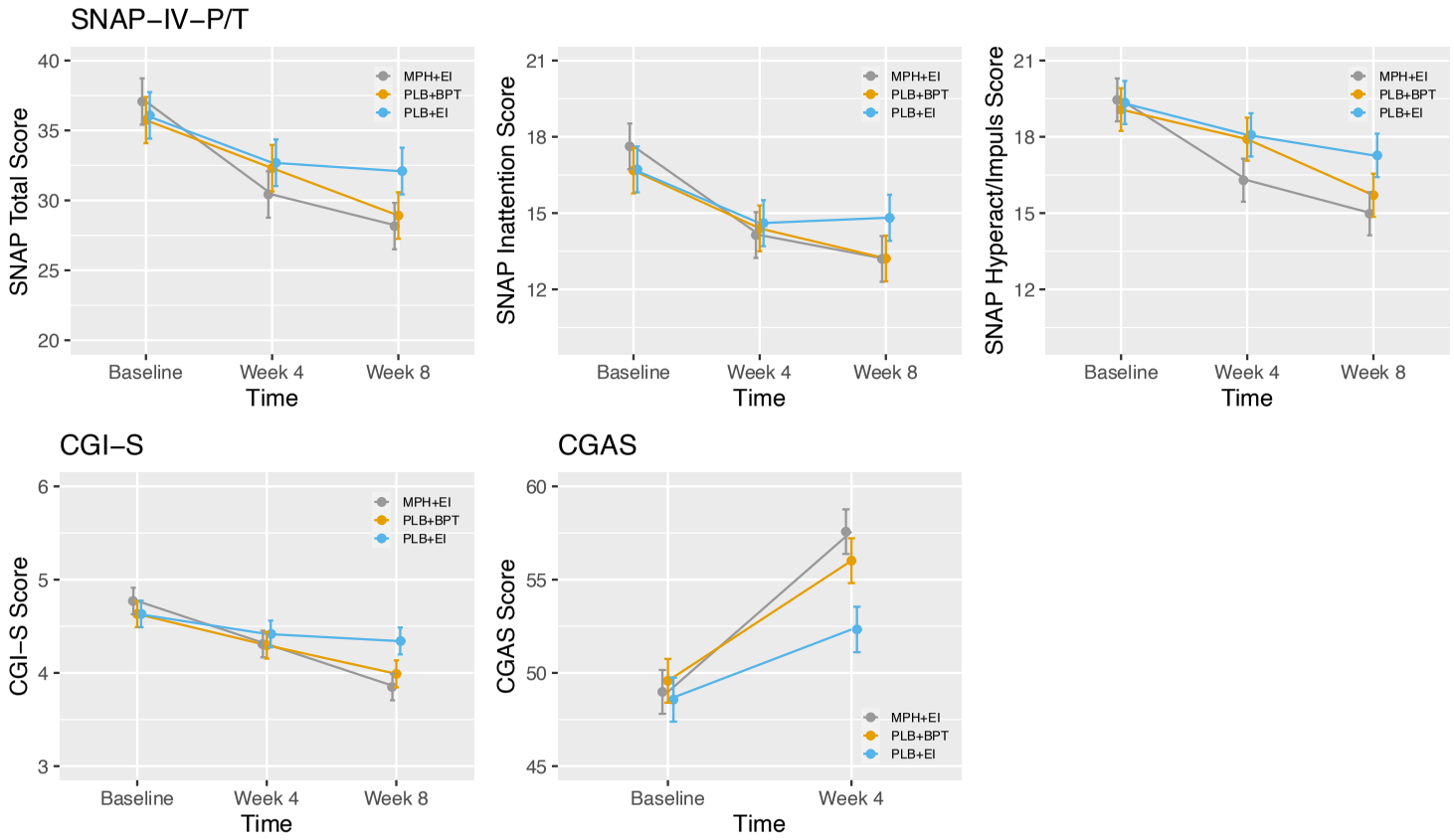
[h] SNAP total scores range from 0 to 54, with higher scores indicating more severe symptoms.

[I] SNAP Inattention score and SNAP Hyperactivity-impulsivity score range from 0 to 27, with higher scores indicating more severe symptoms.

[j] CGI-S scores range from 1 (normal, not at all ill) to 7 (extremely ill).

[k] CGAS scores range from 1-100, with higher scores indicating better global functioning

Figure S2. Changes in primary outcomes by treatment group and time, including only participants with a score of 32 or greater on parent SNAP-IV at the eligibility interview



Abbreviations: CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression – Severity scale; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SNAP-IV, Swanson, Nolan, and Pelham-IV; SNAP-IV-P/T, average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV.
Estimated marginal means from Mixed Effect Models (MEM) analyses are displayed by week and treatment group. Bars indicate standard errors (SE).

Sensitivity analyses using average-scores of parent's and teacher's ratings on the SNAP-IV (SNAP-IV-P/T) and including only teacher's ratings completed by the same teacher at both baseline and outcome assessments.

Due to a protocol deviation, 28 (18.3%) children had different teachers completing the SNAP-IV during the study period. Thus, for sensitivity analyses, the primary outcomes analyses using average scores of SNAP-IV completed parents and teachers including only SNAP-IV-T completed by the same teacher at both baseline and outcome assessments. Similar to the analyses including all teacher SNAP-IV ratings, time by group interactions were detected for: SNAP-IV-P/T total score, SNAP-IV-P/T hyperactivity/impulsivity score, and SNAP-IV-P/T Inattention score. For the SNAP-IV-P/T total score, pairwise comparisons showed significant endpoint differences between MPH+EI vs. PLB+EI (mean difference = -4.06, CI95% -7.32 to -0.81, p-value 0.044, ES = -0·56, CI95%-1·02, -0·11). There was no endpoint difference between groups for specific symptom dimensions (Table S4 and Figure S3).

Table S4. Sensitivity analyses using average scores of parent's and teacher's ratings on the SNAP-IV (SNAP-IV-P/T) and including only teacher's ratings completed by the same teacher at both baseline and outcome assessments [a].

	MPH+EI			PLB+BPT			PLB+EI			Time x Group Inter. P[d]	Results of Pairwise Comparison								
											MPH+EI vs. PLB+BPT			MPH+EI vs. PLB+EI			PLB+BPT vs.PLB+EI		
	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)		Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]
SNAP-IV-P/T [f]																			
Total [g]	36·97 (1·66)	28·16 (1·66)	8·81 (6·80, 10·83)	35·66 (1.66)	28·78 (1·67)	6·88 (4·85, 8·91)	36·01 (1·67)	32·22 (1·68)	3·79 (1·76, 5·82)	0·0025	-0·62 (-3·86, 2·61)	0·71	-0·09 (-0·54, 0.36)	-4·06 (-7·32, -0·81)	0·044	-0·56 (-1·02, -0·11)	-3·44 (-6·70, -0·19)	0·057	-0·48 (-0·93, -0·04)
Inattention [h]	17·58 (0·89)	13·09 (0·89)	4·49 (3·36, 5·61)	16·64 (0.89)	13·07 (0·89)	3·56 (2·43, 4·69)	16·69 (0·89)	14·80 (0·90)	1·89 (0·76, 3·02)	0·0083	0·02 (-1·72, 1·76)	0·98	0·004 (-0·42, 0·43)	-1·71 (-3·46, 0·05)	0·084	-0·42 (-0·85, 0·01)	-1·73 (-3·48, 0·02)	0·084	-0·42 (-0·85, 0·006)
Hyperactivity, Impulsivity [h]	19·41 (0·86)	15·08 (0·87)	4·33 (3·18, 5·47)	19·04 (0·86)	15·72 (0·87)	3·32 (2·16, 4·48)	19·32 (0·87)	17·42 (0·87)	1·90 (0·74, 3·05)	0·014	-0·63 (-2·57, 1·29)	0·52	-0·14 (-0·58, 0·29)	-2·34 (-4·29, -0·40)	0·055	-0·53 (-0·96, -0·09)	-1·70 (-3·65, 0·24)	0·13	-0·38 (0·82, 0·05)

Abbreviations: CI, 95% confidence interval; Mean Diff, mean difference; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SE, standard error; SNAP-IV-P/T, average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV; SNAP-IV-T, Swanson, Nolan, and Pelham-IV completed by teachers

[a] All participants were included in an intent-to-treat analysis. Descriptive statistics reflect the estimated marginal means and proportions from Mixed Effect Models (MEM) analyses. Treatment by time interaction and pairwise comparison results are also based on estimated data from the MEM analyses.

[b] Mean difference between baseline and posttreatment

[c] P value for treatment by time interaction term.

[d] Mean difference between groups in estimated endpoint scores

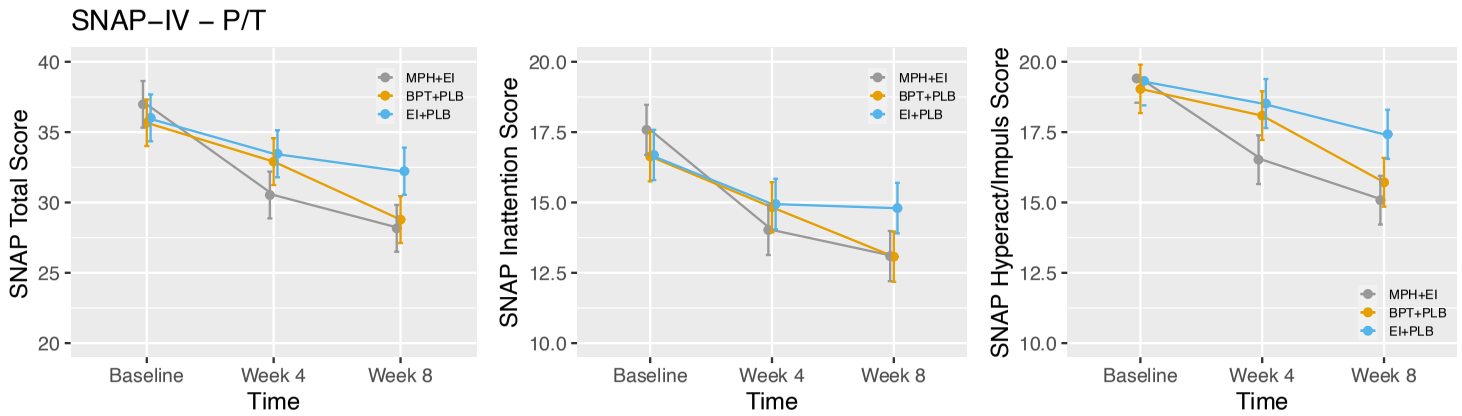
[e] Effect sizes were calculated as standardized mean differences (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at baseline (SD pooled SNAP-IV-P/T Total = 7.20; SD pooled SNAP-IV-P/T Inattention = 4.08, SD pooled SNAP-IV-P/T Hyperactivity/Impulsivity = 4.44).

f SNAP-IV-P/T was computed as average-scores across parents' and teachers' ratings on the Swanson, Nolan, and Pelham-IV, including only outcomes assessments answered by the same teacher at baseline and in the outcome assessments.

g SNAP total scores range from 0 to 54, with higher scores indicating more severe symptoms.

h SNAP Inattention score and SNAP Hyperactivity-impulsivity score range from 0 to 27, with higher scores indicating more severe symptoms.

Figure S3. Changes in average scores of parent's and teacher's ratings on the SNAP-IV (SNAP-IV-P/T) by Treatment Group and Time, including only teacher's ratings completed by the same teacher at both baseline and outcome assessments.



Abbreviations: MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SNAP-IV-P/T, average-scores of Swanson, Nolan, and Pelham-IV completed by parents and teachers; SNAP-IV-T, Swanson, Nolan, and Pelham-IV ratings completed by teachers.
Estimated marginal means from Mixed Effect Models (MEM) analyses are displayed by week and treatment group. Bars indicate standard errors (SE).

Table S5. Missing data on primary outcome variables

	MPH + EI (n=51)	PLB+BPT (n=51)	PLB+EI (n=51)	Total n=153)	p [a]
SNAP-IV-P					
Week 4	1 (2%)	2 (4%)	1 (2%)	4 (3%)	1.0
Week 8	1 (2%)	2 (4%)	2 (4%)	5 (3%)	1.0
Week 4 OR Week 8	1 (2%)	2 (4%)	2 (4%)	5 (3%)	1.0
Week 4 AND Week 8	1 (2%)	2 (4%)	1 (2%)	4 (3%)	1.0
SNAP-IV-T					
Week 4	9 (18%)	11 (22%)	14 (28%)	34 (22%)	0·52
Week 8	9 (18%)	11 (22%)	10 (20%)	30 (20%)	0·97
Week 4 OR Week 8	15 (29%)	18 (35%)	19 (37%)	52 (34%)	0·75
Week 4 AND Week 8	4 (8%)	4 (8%)	6 (12%)	14 (9%)	0·83
CGI-S					
Week 4	1 (2%)	2 (4%)	1 (2%)	4 (3%)	1.0
Week 8	1 (2%)	4 (8%)	2 (4%)	7 (5%)	0·38
CGAS					
Week 8	2 (4%)	3 (6%)	4 (8%)	9 (6%)	0·91

Abbreviations: CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression – Severity scale; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SNAP-IV-P, Swanson, Nolan, and Pelham-IV completed by parents; SNAP-IV-T, Swanson, Nolan, and Pelham-IV completed by teachers.

[a] For comparisons between groups, we used chi-square test of homogeneity. Fisher's Exact Test was used if more than 20% of cells have expected counts below 5.

Table S6. Mean daily dosage of methylphenidate or placebo in each week

		Dosage in mg/kg/day, mean (SD)				P [b]	Absolute Dosage (mg), mean (SD)				p [b]
		MPH + EI	PLB+BPT	PLB+EI	Total		MPH + EI	PLB+BPT	PLB+EI	Total	
Prescribed Dosage											
Week1	0·3	0·30 (0·02)	0·30 (0·01)	0·30 (0·02)	0·30 (0·02)	1·0	6.50 (1.20)	6.94 (1.65)	6.26 (1.19)	6.57 (1.38)	0·044
Week2	0·5	0·50 (0·01)	0·50 (0·03)	0·50 (0·03)	0·50 (0·03)	0·48	10.87 (2.01)	11.46 (2.89)	10.43 (1.84)	10.92 (2.32)	0·08
Week3	0·7	0·69 (0·03)	0·68 (0·11)	0·69 (0·03)	0·69 (0·03)	0·33	15.04 (2.98)	15.31 (4.27)	14.57 (2.60)	14.97 (3.35)	0·55
Week4	0·7	0·70 (0·03)	0·70 (0·08)	0·70 (0·01)	0·70 (0·05)	1·0	15.02 (2.90)	15.98 (3.90)	14.73 (2.72)	15.24 (3.24)	0·14
Week5	1·0 to 1·25	0·99 (0·05)	0·97 (0·13)	0·97 (0·11)	(0·98 (0·10)	0·55	21.37 (4.43)	22.50 (5.17)	21.04 (4.81)	21.61 (4.63)	0·32
Week6		0·99 (0·04)	0·98 (0·12)	0·98 (0·08)	0·99 (0·08)	0·64	21.29 (4.15)	22.50 (5.17)	21.04 (4.48)	21.61 (4.63)	0·26
Week7		1·23 (0·08)	1·23 (0·15)	1·22 (0·11)	1·23 (0·12)	0·97	26.37 (5.37)	28.02 (6.86)	26.19 (5.64)	26.86 (6.00)	0·26
Week8		1·23 (0·12)	1·23 (0·15)	1·23 (0·12)	1·23 (0·12)	1·0	26.22 (5.67)	28.38 (6.88)	26.38 (5.73)	26.99 (6.15)	0·16
Administered Dosage [a]											
Week1	0·3	0·28 (0·06)	0·28 (0·03)	0·29 (0·03)	0·28 (0·04)	0·25	5.94 (1.70)	6.41 (1.54)	5.99 (1.54)	6.11 (1.50)	0.21
Week2	0·5	0·47 (0·06)	0·47 (0·07)	0·46 (0·09)	0·47 (0·07)	0·44	10.34 (2.54)	10.72 (2.92)	9.53 (2.32)	10.20 (2.64)	0·069
Week3	0·7	0·65 (0·08)	0·64 (0·12)	0·67 (0·06)	0·66 (0·09)	0·35	14.26 (3.56)	14.53 (4.14)	14.09 (2.82)	14.29 (3.53)	0·82
Week4	0·7	0·66 (0·07)	0·66 (0·10)	0·67 (0·06)	0·66 (0·08)	0·91	14.35 (3.33)	15.08 (4.07)	14.03 (2.74)	14.49 (3.43)	0·30
Week5	1·0 to 1·25	0·92 (0·20)	0·91 (0·14)	0·95 (0·12)	(0·93 (0·16)	0·61	20.03 (6.12)	20.92 (5.35)	20.04 (4.22)	20.33 (5.27)	0·64
Week6		0·94 (0·12)	0·95 (0·13)	0·95 (0·10)	0·95 (0·12)	0·82	20.13 (4.65)	21.83 (5.25)	20.26 (4.39)	20.74 (4.81)	0·15
Week7		1·14 (0·21)	1·15 (0·18)	1·17 (0·16)	1·16 (0·19)	0·75	24.66 (6.87)	26.36 (6.49)	25.13 (6.57)	25.38 (6.64)	0·43
Week8		1·16 (0·13)	1·14 (0·26)	1·18 (0·14)	1·16 (0·19)	0·55	25.00 (6.15)	25.86 (8.09)	25.45 (6.05)	25.45 (6.77)	0·83

Abbreviations: MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention

[a] Administered dosage was the prescribed dosage minus the residual medication returned to study pharmacist in each week.

[b] For comparisons between groups, we used one-way ANOVA.

Table S7. Participants not following the dosing schedule

	MPH + EI (N=51)	PLB+BPT (N=51)	PLB+EI (N=51)	Total (N=153)	P [a]
Weeks 1-4					
Dosage was maintained and not increase	1 (2%)	2 (4%)	1 (2%)	4 (3%)	0·94
Dosage was decreased	1 (2%)	1 (2%)	0	2 (1%)	
Drop-out	1 (2%)	2 (4%)	2 (4%)	5 (3%)	
Weeks 5-8					
Dosage <1.0 mg/kg/d was maintained	1 (2%)	3 (6%)	0	4 (3%)	0·38
Dosage was decreased	2 (4%) [b]	0	3 (6%)	5 (3%)	
Drop-out	1 (2%)	1 (2%)	2 (4%)	4 (3%)	
Dosage at week 8					
<1.00 mg/kg/day	0	1 (2%)	2 (4%)	3 (2%)	0·56
Drop-out	2 (4%)	3 (6%)	4 (8%)	9 (6%)	

Abbreviations: MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention

[a] For comparisons between groups, we used chi-square test of homogeneity. Fisher's Exact Test was used if more than 20% of cells have expected counts below 5.

[b] For both children dosage was decreased from 1.25 to 1.0.

Sensitivity analyses: SNAP-IV-P and SNAP-IV-T ratings analyzed separately

As described above (see Parents and teachers' ratings integration), for the primary outcome analyses, we computed average-scores across parent and teacher ratings of ADHD symptoms on the SNAP-IV. As sensitivity analyses, we repeated the analyses for the SNAP-IV-P and SNAP-IV-T ratings separately.

By parent report, there were time by group interactions for SNAP-IV-P total score and SNAP-IV-P hyperactivity/impulsivity score. For SNAP-IV-P total score, there were endpoint differences between MPH+EI vs. PLB+EI (mean difference= -5.87, CI95% -9.34 to -2.40, p-value 0.0029, ES = -0·73, CI95% -1·17, -0·30), and between PLB+BPT vs. PLB+EI (mean difference= -4.21, CI95% -7.68 to -0.75, p-value 0.026, ES = -0·53, CI95% -0·78, -0·08). For SNAP-IV-P hyperactivity-impulsivity score, there was an endpoint difference between MPH+EI vs. PLB+EI (mean difference= -3.31, CI95% -5.30 to -1.31, p-value 0.0037, ES = -0·71, CI95% -1·14, -0·28). Although the time by group interaction was not significant for SNAP-IV-P inattention, there were endpoint differences between MPH+EI vs. PLB+EI (mean difference= -2.55, CI95% -4.41 to -0.70, p-value 0.017, ES = -0·59, CI95% -1·01, -0·16) and between PLB+BPT vs. PLB+EI (mean difference= -2.38, CI95% -4.24 to -0.53, p-value 0.017, ES = -0·55, CI95% -0·98, -0·12). By teacher report, time by group interactions were not significant (Table S8, Figure S4).

Table S8. Sensitivity analyses: SNAP-IV-P and SNAP-IV-T ratings analyzed separately [a]

	MPH+EI			PLB+BPT			PLB+EI			Time x Group Inter. P[d]	Results of Pairwise Comparison								
											MPH+EI vs. PLB+BPT			MPH+EI vs. PLB+EI			PLB+BPT vs.PLB+EI		
	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)		Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]
SNAP-IV-P [f]																			
Total [g]	37·83 (1·57)	27·13 (1·58)	10·70 (8·33, 13·06)	37·61 (1.57)	28·79 (1·58)	8·82 (6·44, 11·20)	38·04 (1·58)	33·00 (1·59)	5·04 (2·66, 7·42)	0·019	-1·66 (-5·10, 1·79)	0·35	-0·20 (-0·64, 0·22)	-5·87 (-9·34, -2·40)	0·0029	-0·73 (-1·17, -0·30)	-4·21 (-7·68, -0·75)	0·026	-0·53 (-0·78, -0·08)
Inattention [h]	17·79 (0·92)	12·54 (0.92)	5·25 (3·97, 6·54)	17·33 (0·92)	12·71 (0·92)	4·62 (3·33, 5·92)	17·80 (0·92)	15·09 (0·93)	2·71 (1·41, 4·01)	0·069	-0·17 (-2·01, 1·67	0·86	-0·04 (-0·46, 0·39)	-2·55 (-4·41, -0·70)	0·017	-0·59 (-1·01, -0·16)	-2·38 (-4·24, -0·53)	0·017	-0·55 (-0·98, -0·12)
Hyperactivity, Impulsivity [h]	20·07 (0·76)	14·63 (0·77)	5·44 (4·10, 6·79)	20·30 (0·76)	16·11 (0·77)	4·19 (2·84, 5·55)	20·26 (0·77)	17·93 (0·77)	2·33 (0·97, 3·68)	0·032	-1·48 (-3·47, 0·50)	0·14	-0·31 (-0·74, 0·11)	-3·31(-5·30, -1·31)	0·0037	-0·71 (-1·14, -0·28)	-1·83 (-3·82, 0·17)	0·11	-0·39 (-0·82, 0·04)
SNAP-IV-T [i]																			
Total [g]	35·96 (2·60)	29·95 (2·65)	6·01 (3·17, 8·85)	33·88 (2·59)	29·96 (2·66)	3·92 (1·05, 6·79)	33·63 (2·60)	31·90 (2·66)	1·73 (-1·13, 4·60)	0·063	-0·008 (-4·89, 4·88)	1.0	-0·0007 (-0·44, 0·44)	-1·95 (-6·84, 2·94)	0·65	-0·18 (-0·62, 0·27)	-1·94 (-6·85, 2·96)	0·65	-0·18 (-0·62, 0·27)
Inattention [h]	17·33 (1·28)	14·42 (1·30)	2·91 (1·43, 4·38)	16·11 (1·27)	14·21 (1·31)	1·90 (0·40, 3·39)	15·37 (1·28)	15·13 (1·31)	0·24 (-1·25, 1·74)	0·065	0·21 (-2·43, 2·85)	0·87	0·03 (-0·39, 0·45)	-0·70 (-3·34, 1·94)	0·87	-0·11 (-0·53, 0·31)	-0·91 (-3·56, 1·73)	0·87	-0·15 (-0·57, 0·28)
Hyperactivity Impulsivity [h]	18·63 (1·43)	15·52 (1·47)	3·10 (1·36, 4·85)	17·76 (1·43)	15·72 (1·47)	2·04 (0·27, 3·81)	18·21 (1·43)	16·72 (1·47)	1·49 (-0·27, 3·25)	0·14	-0·20 (-3·17, 2·78)	0·90	-0·03 (-0·45, 0·40)	-1·20 (-4·18, 1·78)	0·76	-0·17 (-0·60, 0·25)	-1·00 (-3·99, 1·99)	0·76	-0·14 (-0·57, 0·28)

Abbreviations: CI, 95% confidence interval; ES, effect size; Mean Diff, mean difference; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SE, standard error; SNAP-IV-P, Swanson, Nolan, and Pelham-IV completed by parent; SNAP-IV-T, Swanson, Nolan, and Pelham-IV completed by teachers.

[a] Descriptive statistics reflect the estimated marginal means and proportions from Mixed Effect Models (MEM) analyses. Treatment by time interaction and pairwise comparison results are also based on estimated data from the MEM analyses.

[b] Mean difference between baseline and posttreatment

[c] P value for treatment by time interaction term.

[d] Mean difference between groups in estimated endpoint scores

[e] Effect sizes were calculated as standardized mean differences (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at baseline (SD pooled SNAP-IV-P Total = 8.01; SD pooled SNAP-IV-P Inattention = 4.34; SD pooled SNAP-IV-P Hyperactivity/Impulsivity = 4.67; SD pooled SNAP-IV-T Total = 11.07; SD pooled SNAP-IV-T Inattention = 6.27, SD pooled SNAP-IV-T Hyperactivity/Impulsivity = 6.99).

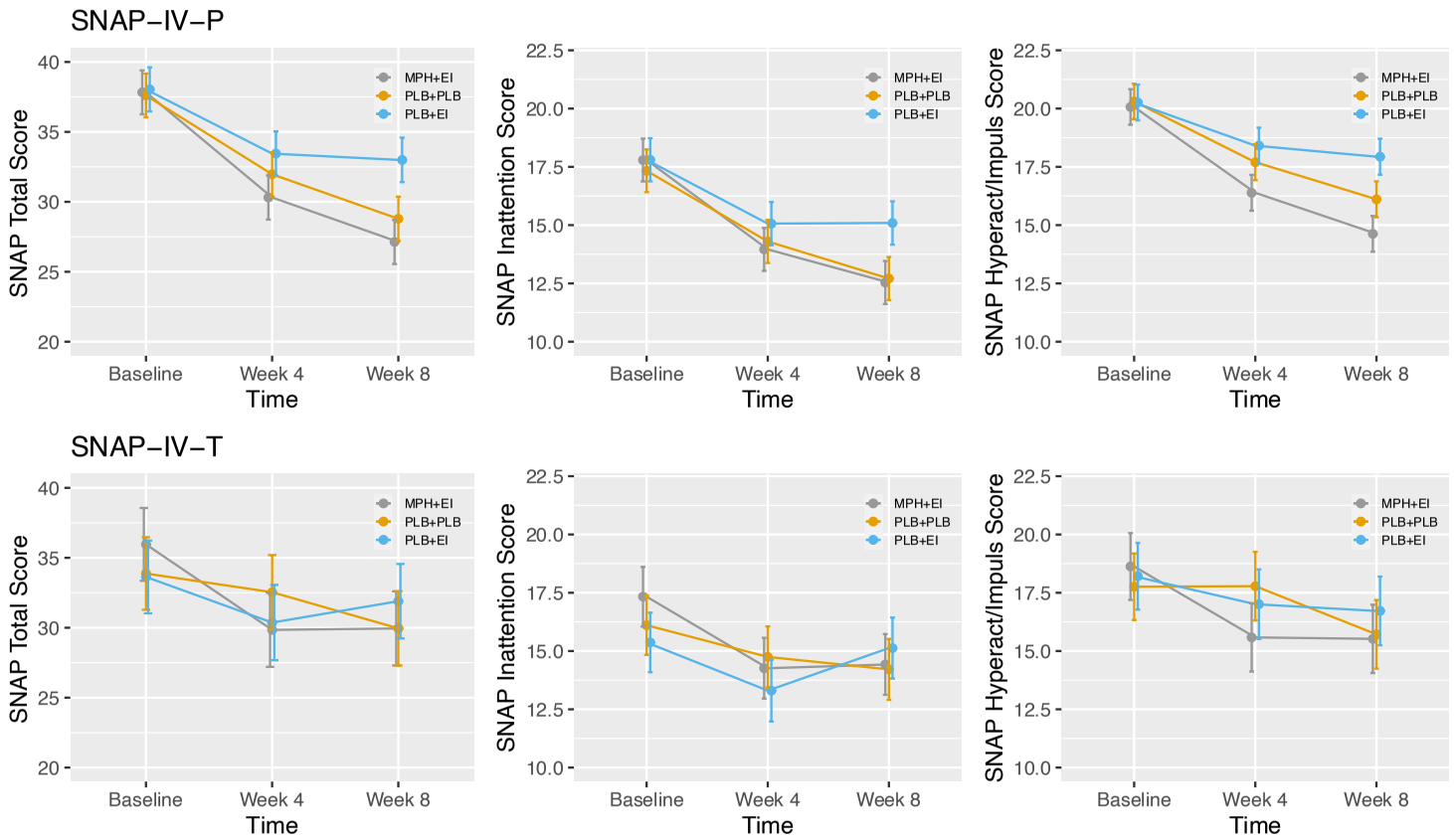
[f] All participants were included in an intent-to-treat analysis.

[g] SNAP total scores range from 0 to 54, with higher scores indicating more severe symptoms.

[h] SNAP Inattention score and SNAP Hyperactivity-impulsivity score range from 0 to 27, with higher scores indicating more severe symptoms.

[i] Analyses were conducted using data from all teachers. 2 participants did not have teachers' baseline and outcome assessments (n=50 MPH+EI; n=50 PLB+BPT; n=51 PLB+EI)

Figure S4. Changes in SNAP-IV-P and SNAP-IV-T ratings by treatment group and time



Abbreviations: MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SNAP-IV-P, Swanson, Nolan, and Pelham-IV completed by parents; SNAP-IV-T, Swanson, Nolan, and Pelham-IV completed by teachers. Estimated marginal means from Mixed Effect Models (MEM) analyses are displayed by week and treatment group. Bars indicate standard errors (SE).

Secondary outcomes analyses – K-CPT-2

Because of a high number of omissions, the K-CPT program was not able to compute the 'variability' score in part of the K-CPT-2 tests. To ensure test validity, we performed the analyses including only K-CPT-2 tests with complete measures (Baseline: N=83; Posttreatment: N=88; MPH+EI: N=38; PLB+BPT: N=37; PLB+EI: N=39); and K-CPT-2 tests without the 'variability' score were treated as missing. For sensitivity analyses, we repeated the analyses, except for the measure 'variability', including all KCPT tests (Baseline: N=145; Posttreatment: N=130, MPH+EI: N=49; PLB+BPT: N=51; PLB+EI: N=50).

In the analyses including only the data from K-CPT-2 tests with complete measures (Table S9), time by group interactions were documented for detectability, Hit reaction time Standard Deviation (HRT-SD), and commissions. For detectability and HRT-SD, pairwise comparisons showed significant endpoint differences between MPH+EI and PLB+BPT (detectability: mean difference= -5.36, CI95% -8.65, to -2.08, p-value 0.0046, ES = -0·92, CI95% -1·48, -0·36); HRT SD: mean difference= -9.04, CI95% -15.51 to -2.58, p-value 0.016, ES = -0·74 , CI95% -1·27, -0·21); and between MPH+EI and PLB+EI (detectability: mean difference= -4.83, CI95% -8.22 to -1.45, p-value 0.0081, ES = -0·83, CI95% -1·41, -0.25; HRT SD: mean difference= -8.67, CI95% -15.33 to -2.02, p-value 0.016, ES = -0·71, CI95% -1·25, -0·17). No significant endpoint differences between groups were found for commissions.

In the sensitivity analyses including data from all K-CPT-2 tests (Table S9), time by group interactions were detected for detectability, HRT-SD, and omission. For detectability, HRT-SD, and omission, pairwise comparisons showed significant endpoint differences between MPH+EI and PLB+BPT (Detectability: mean difference= -5.28, CI95% -7.88 to -2.67, p-value 0.0002, ES = -0·78, CI95% -1·16, -0·39; HRT-SD: mean difference= -9.44, CI95% -14,67 to -4.22, p-value 0.0013, ES = -0·77, CI95% -1·20, -0·34; Omission: mean difference= -11.40, CI95% -17.57 to -5.22, p-value 0.0010, ES = -0·76, CI95% -1·18, -0·35); and between MPH+EI and PLB+EI (Detectability: mean difference= -5.01, CI95% -7.69 to -2.32, p-value 0.0004, ES = -0·74, CI95% -1·13, -0·34; HRT-SD: mean difference= -9.13, CI95% -14.51 to -3.74, p-value 0.0014, ES = -0·75, CI95% -1·18, -0·31; Omission: mean difference= -9.12, CI95% -15.50 to -2.75, p-value 0.0078, ES = -0·61, CI95% -1·04, -0·18).

Table S9. Secondary Outcomes Analyses – K-CPT-2 [a]

	MPH+EI			PLB+BPT			PLB+EI			Time x Group Inter. p[c]	Results of Pairwise Comparison								
											MPH+EI vs. PLB+BPT			MPH+EI vs. PLB+EI			PLB+BPT vs. PLB+EI		
	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)		Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]
K-CPT-2 (Complete tests) [f, g]																			
Detectability	64·49 (1·37)	56·64 (1·09)	7·86 (4·97, 10·74)	62·53 (1·23)	62·00 (1·25)	0·53 (-2·41, 3·47)	64·82 (1·15)	61·47 (1.31)	3·35 (0·41, 6·29)	0·0026	-5·36 (-8·65, -2·08)	0·0046	-0·92 (-1·48, -0·36)	-4·83 (-8·22, -1·45)	0·0081	-0·83 (-1·41, -0.25)	0·53 (-3·04, 4·11)	0·77	0·09 (-0·52, 0·70)
Omission	63·43 (2·71)	60·74 (2·14)	2·68 (-3·34, 8·70)	66·81 (2·43)	69·64 (2·46)	-2·82 (-8·89, 3·24)	65·73 (2·26)	64·88 (2·59)	0·85 (-5·20, 6·91)	0·43	-8·89 (-15·08, -2·70)	0·015	-0·59 (-1·01, -0·18)	-4·14 (-10·52, 2·25)	0·20	-0·28 (-0·70, 0·15)	4·76 (-2·03, 11·54)	0·20	0·32 (-0·14, 0·77)
Hit Reaction Time SD	70·01 (2·68)	61·16 (2·15)	8·86 (3·21, 14·50)	68·52 (2·41)	70·20 (2·45)	-1·68 (-7·44, 4·07)	72·52 (2·26)	69·83 (2·58)	2·69 (-3·07, 8·45)	0·0374	-9·04 (-15·51, -2·58)	0·016	-0·74 (-1·27, -0·21)	-8·67 (-15·33, -2·02)	0·016	-0·71 (-1·25, -0·17)	0·37 (-6·65, 7·39)	0·92	0·03 (-0·54, 0·60)
Hit Reaction Time	59·50 (1·97)	61·90 (1·61)	-2·39 (-6·33, 1·54)	59·57 (1·80)	60·98 (1·82)	-1·41 (-5·41, 2·59)	58·46 (1·69)	58·60 (1·90)	-0·14 (-4·13, 3·85)	0·73	0·92 (-3·46, 5·30)	0·68	0·10 (-0·37, 0·57)	3·30 (-1·21, 7·82)	0·45	0·36 (-0·13, 0.84)	2·38 (-2·39, 7·14)	0·49	0·26 (-0·26, 0·77)
Commission	61·14 (1·95)	50·92 (1·63)	10·23 (6·58, 13·87)	57·38 (1·81)	54·88 (1·82)	2·50 (-1·23, 6·23)	61·30 (1·70)	56·00 (1·89)	5·30 (1·57, 9·02)	0·014	-3·96 (-8·37, 0·45)	0.12	-0·36 (-0·76, 0·04)	-5·08 (-9·61, -0·55)	0·084	-0·46 (-0·88, -0·05)	-1·13 (-5·88, 3·63)	0·64	-0·10 (-0·54, 0·33)
Perseveration	67·51 (3·39)	57·78 (2·69)	9·72 (2·25, 17·21)	65·89 (3·04)	66·28 (3·09)	-0·38 (-7·94, 7·18)	72·53 (2·83)	65·81 (3·25)	6·72 (-0·83, 14·26)	0·16	-8·50 (-16·31, -0·69)	0·075	-0·56 (-1·08, -0·05)	-8·04 (-16·09, 0·01)	0·075	-0·53 (-1·07, 0·0008)	0·46 (-8·08, 9·01)	0·91	0·03 (-0·53, 0·60)
Variability	69·20 (4·69)	63·40 (4·36)	3·30 (-2·47, 9·08)	68·17 (4·51)	73·14 (4·51)	-5·41 (-11·23, 0·41)	69·23 (4·47)	70·22 (4·62)	1·83 (-3·98, 7·64)	0·084	-7·86 (-13·70, -2·03)	0·026	-0·73 (-1·27, -0·19)	-5·11 (-11·13, 0·90)	0·14	-0·47 (-1·03, 0·08)	2·75 (-3·66, 9·15)	0·40	0·25 (-0·34, 0·84)
K-CPT -2 (All tests) [f, h]																			
Detectability	65·68 (0·94)	58·04 (0·94)	7·64 (5·63, 9·66)	64·42 (0·89)	63·31 (0·93)	1·11 (-0·84, 3·05)	65·27 (0·91)	63·04 (0·98)	2·23 (0·17, 4·28)	<0·0001	-5·28 (-7·88, -2·67)	0·0002	-0·78 (-1·16, -0·39)	-5·01 (-7·69, -2·32)	0·0004	-0·74 (-1·13, -0·34)	0·27 (-2·40, 2·94)	0·84	0·04 (-0·35, 0·43)
Omission	75·91 (2·38)	65·65 (2·38)	10·27 (5·17, 15·37)	77·00 (2·26)	77·04 (2·38)	-0·04 (-4·96, 4·88)	73·05 (2·33)	74·77 (2·50)	-1·72(-6·90, 3·47)	0·0023	-11·40 (-17·57, -5·22)	0·0010	-0·76 (-1·18, -0·35)	-9·12 (-15·50, -2·75)	0·0078	-0·61 (-1·04, -0·18)	2·27 (-4·06, 8·60)	0·48	0·15 (-0·27, 0·58)
Hit Reaction Time	71·84	62·21	9.64	71·55	71·76	-0·09, -	72·11	71·32	(0·79, -	0·0012	-9·44 (-	0·00	-0·77 (-	-9·13,	0·00	-0·75 (-	0·31 (-	0·91	0·03 (-

SD	(1·88)	(1·88)	(5.61, 13.68)	(1·77)	(1·89)	3·98, 3·80)	(1·82)	(1·97)	3·33, 4·90)		14·67, -4·22)	13	1·20, -0·34)	(-14·51, -3·74)	14	1·18, -0·31)	5·03, 5·66)		0·41, 0·46)
Hit Reaction Time	61·65 (1·73)	62·64 (1·73)	-1.00 (-4.20, 2.20)	61·48 (1·66)	62·53 (1·73)	-1·05 (-4·13, 2·04)	61·09 (1·71)	60·42 (1·81)	0·66 (-2·59, 3·92)	0·70	0·12 (-3·91, 4·14)	0·96	0·01 (-0·42, 0·45)	2·22 (-1·94, 6·38)	0·47	0·24 (-0·21, 0·69)	2·10 (-2·02, 6·23)	0·47	0·23 (-0·22, 0·67)
Commission	54·03 (1·94)	49·51 (1·94)	4.52 (1.26. 7.79)	52·10 (1·88)	50·61 (1·94)	1·48 (-1·67, 4·63)	57·06 (1·92)	50·91 (2·02)	6·15, 2·82, 9·48)	0·12	-1·09 (-5·33, 3·15)	0·89	-0·10 (-0·49, 0·28)	-1·40 (-5·76, 2·95)	0·89	-0·13 (-0·53, 0·27)	-0·31 (-4·65, 4·02)	0·89	-0·03 (-0·42, 0·37)
Perseveration	64·74 (2·60)	57·62 (2·60)	7.12 (1.64, 12.60)	64·44 (2·48)	63·98 (2·62)	0·43 (-4·86, 5·73)	68·26 (2·55)	64·51 (2·72)	3·75 (-1·82, 9·31)	0·23	-6·39 (-12·58, -0·20)	0·065	-0·42 (-0·83, -0·01)	-6·89 (-13·29, -0·49)	0·065	-0·46 (-0·88, -0·03)	-0·50 (-6·86, 5·85)	0·88	-0·03 (-0·46, 0·39)

Abbreviations: CI, 95% Confidence Interval; ES, Effect Size; HRK-CPT-2, Conners Kiddie Continuous Performance Test; Mean Diff, Mean Difference; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SD, Standard Deviation; SE, Standard Error.

[a] Descriptive statistics reflect the estimated marginal means and proportions from Mixed Effect Models (MEM) analyses. Treatment by time interaction and pairwise comparison results are also based on estimated data from the MEM analyses.

[b] Mean difference between baseline and posttreatment

[c] P value for treatment by time interaction term.

[d] Mean difference between groups in estimated endpoint scores

[e] Effect sizes were calculated as standardized mean differences (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at baseline (SD pooled detectability = 5.84; SD pooled omission = 14.95; SD pooled commission = 10.96; SD pooled reaction tine = 9.27; SD pooled reaction time SD = 12.25; SD pooled perseveration = 15.07; SD pooled variability = 10.80).

[f] For each variable K-CPT-2 generates T-scores. High scores for Detectability (d'), Omissions and Commissions, Hit reaction Time (HRT), Hit Reaction Time Standard Deviation (HRT-SD) and Variability are indicators of inattentiveness. Low scores for HRT, in addition to high Commissions and/or Perseverations, are indicators of impulsivity.

[g] Only K-CPT-2 tests with complete measures were included in the analyses (Baseline: N=83; Posttreatment N=88, n=38 MPH+EI; n=37 PLB+BPT; n=39 PLB+EI)

[h] All K-CPT-2 tests were included in the analyses (Baseline: N=145; Posttreatment N=130; n=49 MPH+EI; n=51 PLB+BPT; n=50 PLB+EI)

Secondary outcomes analyses – irritability and disruptive behavior

Disruptive behaviors and irritability are frequently associated with ADHD and major clinical complaints. Therefore, we investigated these symptoms with two well validated measures, the Affective Reactivity Index (ARI) and the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB).

For the ARI score, significant time by group interaction was detected and significant endpoint differences were observed between PLB+BPT and PLB+EI (mean difference= -1.60, CI95% -2.81 to -0.39, p-value 0.029, ES = -0·50, CI95% -0·88, -0·12) (Table S10). For the MAP-DB, time by group interaction was detected for the Temper Loss dimension and significant endpoint differences were observed between MPH+EI and PLB+BPT (mean difference= 8.85, CI95% 1.57, 16.13, p-value 0.026, ES = 0·43, CI95% 0·08, 0·77); and PLB+BPT and PLB+EI (mean difference= -14.08, CI95% -21.46 to -6.70, p-value 0.0006, ES = -0·68, CI95% -1·03, -0·32) (Table S10).

Table S10. Secondary Outcomes Analyses – irritability and disruptive behavior [a]

	MPH+EI			PLB+BPT			PLB+EI			Time x Group Inter. p[c]	Results of Pairwise Comparison								
											MPH+EI vs. PLB+BPT			MPH+EI vs. PLB+EI			PLB+BPT vs. PLB+EI		
	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)		Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]
ARI Score [f]	6·11 (0·43)	4·66 (0·43)	1·45 (0·67, 2·23)	5·75 (0·43)	3·95 (0·44)	1·80 (1·01, 2·58)	5.95 (0.43)	5·55 (0·44)	0·40 (-0·40, 1·19)	0·039	0·71 (-0.50, 1.91)	0·25	0·22 (-0·16, 0·60)	-0·89 (-2·10, 0·32)	0·22	-0·28 (-0·66, 0·10)	-1·60 (-2·81, -0·39)	0·029	-0·50 (-0·88, -0·12)
MAP-DB																			
Temper Loss	36·81 (2·57)	26·81 (2·59)	10·07 (4.28, 15·73)	33·31 (2·57)	17·96 (2·63)	15·35 (9·55, 21·16)	34·69 (2·58)	32·04 (2·67)	2·66 (-3·19, 8·51)	0·010	8·85 (1·57, 16·13)	0·026	0·43 (0·08, 0·77)	-5·23 (-12·57, 2·11)	0·16	-0·25 (-0·60, 0·10)	-14·08 (-21·46, -6·70)	0·0006	-0·68 (-1·03, -0·32)
Low Concern to Others	15·06 (1·14)	11·24 (1·14)	3·83 (1·49, 6·17)	14·20 (1·13)	8·29 (1·16)	5·92 (3·54-8·29)	16·11 (1·14)	12·25 (1·17)	3·86 (1·47, 6·26)	0·37	2·95 (-0·26, 6·16)	0·11	0·32 (-0·03, 0·66)	-1·01 (-4·25, 2·22)	0·54	-0·10 (-0·46, 0·24)	-3·96 (-7·22, -0·71)	0·051	-0·43 (-0·78, -0·08)
Non-compliance	54·06 (3·45)	43·06 (3·45)	11·10 (4·62, 17·58)	55·31 (3·46)	34·61 (3·51)	20·10 (13·48, 26·71)	58·91 (3·44)	47·55 (3·53)	11·36 (4·74, 17·99)	0·098	7·81 (-0·78, 16·40)	0·11	0·33 (-0·03, 0·68)	-4·43 (-13·11, 4·24)	0·32	-0·19 (-0·55, 0·18)	-12·24, -20·95, -3·53)	0·018	-0·51 (-0·87, -0·15)
Aggression	22·67 (2·29)	16·11 (2·29)	6·55 (2·52, 10·57)	18·19 (2·30)	11·99 (2·33)	6·03 (1·91, 10·16)	20·00 (2·27)	17·45 (2·33)	2·54 (-1·58, 6·67)	0·34	4·09 (-2·31, 10·49)	0·31	0·23 (-0·13, 0·59)	-1·36 (-7·79, 5·07)	0·68	-0·08 (-0·44, 0·29)	-5·45 (-11·91, 1·02)	0·29	-0·31 (-0·67, 0·06)
Insensitivity to punishment	14·47 (1·09)	11·07 (1·10)	3·40 (1·17, 5·64)	14·08 (1·09)	9·08 (1·11)	4·99 (2·72, 7·26)	15·37 (1·09)	12·01 (1·13)	3·35 (1·07, 5·63)	0·52	1·98 (-0·96, 4·93)	0·28	0·24 (-0·12, 0·61)	-0·95 (-3·92, 2·02)	0·53	-0·12 (-0·48, 0·25)	-2·93 (-5·92, 0·06)	0·16	-0·36 (-0·73, 0·007)

Abbreviations: ARI, Affective Reactivity Index; CI, 95% Confidence Interval; ES, Effect Size; MAP-DB Multidimensional Assessment of Preschool Disruptive Behavior; Mean Diff, Mean Difference; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SE, Standard Error.

[a] All participants were included in an intent-to-treat analysis. Descriptive statistics reflect the estimated marginal means and proportions from Mixed Effect Models (MEM) analyses. Treatment by time interaction and pairwise comparison results are also based on estimated data from the MEM analyses.

[b] Mean difference between baseline and posttreatment

[c] P value for treatment by time interaction term.

[d] Mean difference between groups in estimated endpoint scores

[e] Effect sizes were calculated as standardized mean differences (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at baseline (SD pooled ari = 3.18; SD pooled map-db low concern = 9.29; SD pooled map-db temper loss = 20.86; SD pooled map-db noncompliance = 23.95; SD pooled map-db aggression = 17.77; SD pooled map-db insensitivity to punishment = 8.12).

[f] The Affective Reactivity Index (ARI) scores range from 0 to 12, with higher scores indicating more severe irritability.

[g] The Multidimensional Assessment Profile of Disruptive Behaviors (MAP-DB), assesses 5 dimensions: low concern to others (range: 0-45), temper loss (range: 0-110), aggression (range: 0-125), noncompliance (range: 0-110) and insensitivity to punishment (range: 0-35), with higher scores indicating more severe symptomatology.

Table S11. Adverse events reported by parents during clinical evaluations: number of times that each adverse event was reported during treatment

	MPH + EI	PLB+BPT	PLB+EI	Total	p[a]
Mild Adverse Events [b], No.					
Decreased Appetite	65	29	25	119	<0·0001[c]
Increased appetite	0	10	6	16	0·0049[f]
Decreased Weight	5	2	0		0·065
Insomnia	27	12	14	53	0·032[g]
Restless sleep	8	9	7	24	0·83
Night awakenings	3	4	7	1	0·41
Drowsiness	3	5	5	13	0·69
Nightmares	1	5	4	10	0·21
Changes in sleeping habits during daytime	2	1	3	6	0·70
Headache	13	11	3	27	0·014[h]
Fever	5	2	4	11	0·64
Tiredness / fatigue	2	4	2	8	0·61
Abdominal pain	13	10	9	32	0·74
Diarrhea	4	6	9	19	0·33
Constipation	4	5	1	10	0·25
Changes in Bowel habits (increase)	1	1	0	2	0·77
Vomiting	2	3	9	14	0·069
Nausea	3	1	1	5	0·63
Cough	9	10	8	27	0·84
Runny nose	9	9	5	23	0·48
Cold symptoms	6	4	3	13	0·65
Sore Throat	1	1	1	3	1·0
Rhinitis	0	1	1	2	0·55
Earache	1	0	1	2	1·0
Increases Heart-rate	4	1	2	7	0·52
Chest Pain	2	2	0	4	0·47
Palpitation	1	2	0	3	0·43
Dermatologic symptoms	3	4	5	12	0·72
Itching	2	3	4	9	0·65
Picking at skin or nails	2	0	0	2	0·33
Lip biting	3	0	0	3	0·11
Enuresis	2	4	2	8	0·61
Encopresis	2	0	3	5	0·33
Tics	2	1	2	5	1·0
Stereotyped movement	0	2	1	3	0·21
Pain (legs, knee or feet)	2	2	0	4	0·47
Epistaxis	1	2	0	3	0·43
Dry mouth	0	1	1	2	0·55
Thirst	1	1	0	2	0·77
Increased genital manipulation	1	1	0	2	0·77
Prone to crying[SEP]	15	9	3	27	0·021[i]
Anxiety	5	3	4	12	0·93
Irritability	29	14	19	62	0·082
Aggressive behavior	14	10	4	28	0·070
Defiant behavior / opposition	10	7	10	27	0·78
Increased Hyperactivity	25	13	23	61	0·16
Increased Impulsivity	2	0	1	3	0·78
Increased Inattention	0	1	1	2	0·55
Sleepwalking	0	0	1	1	0·65
Stomachache	1	0	0	1	1·0

Bloated abdomen	0	0	1	1	0·65
Change in bowel habits (reduction)	0	1	0	1	0·32
Flatulence	0	1	0	1	0·32
Food poisoning	0	0	1	1	0·65
Dizziness	1	0	0	1	1·0
Increased sweating	0	0	1	1	0·65
Bites finger nails	1	0	0	1	1·0
Hair Loss	0	0	1	1	0·65
Dry Lips	1	0	0	1	1·0
Acne	1	0	0	1	1·0
Oral lesions	0	1	0	1	0·32
Diplopia	1	0	0	1	1·0
Anguish	0	0	1	1	0·65
Disengagement from activities	0	0	1	1	0·65
Euphoria	0	0	1	1	0·65
Muscle weakness (transient)	0	0	1	1	0·65
Paresthesia (transient)	1	0	0	1	1·0
Starring	1	0	0	1	1·0
Pain in forehead	1	0	0	1	1·0
Facial flush	1	0	0	1	1·0
Red ears	0	0	1	1	0·65
Biting objects	1	0	0	1	1·0
Moderate adverse events [c], No. (%)					
Abdominal pain	1	2	0	3	0·43
Diarrhea	0	2	1	3	0·21
Constipation	0	1	0	1	0·32
Vomiting	0	1	1	2	0·55
Headache	1	5	1	7	0·14
Fever	2	3	2	7	0·80
Tiredness/fatigue	0	0	1	1	0·65
Dizziness	0	0	1	1	0·65
Runny nose	1	0	1	2	1·0
Cough	1	0	1	2	1·0
Pharyngitis / tonsillitis	2	1	1	4	1·0
Sinusitis	0	1	0	1	0·32
Difficulty breathing	2	0	0	2	0·33
Skin changes	1	1	1	3	1·0
Itching	0	1	0	1	0·32
Atopy	1	0	0	1	1·0
Anal bleeding	0	0	2	2	0·21
Urinary infection	0	1	0	1	0·32
Physical trauma (accidents)	1	1	0	2	0·77
Severe adverse events [d], No. (%)					
Asthma exacerbation	1	0	0	1	1·0
H1N1	0	1	0	1	0·32

Abbreviations: MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention.

[a] We used chi-square test of homogeneity, and multiple z-tests of two proportions with Bonferroni correction for pairwise comparisons, were used. If more than 20% of cells have expected counts below 5. If more than 20% of cells have expected counts below 5, we used Fisher's Exact Test.

[b] Adverse events were classified as 'mild' if not required any further action.

[c] Adverse events were classified as 'moderate' if required medical evaluation or interventions (e.g., dosage adjustment or the use of an over-the-counter medication).

[d] Adverse events were classified as 'severe' if required hospitalization or represented a serious medical threat (e.g., seizure).

[e] Pairwise comparisons: MPH+EI > PLB+BPT, PLB+EI
[f] Pairwise comparisons: MPH+EI < PLB+BPT, PLB+EI
[g] Pairwise comparisons: MPH+EI > PLB+BPT, PLB+EI
[h] Pairwise comparisons: MPH+EI > PLB+EI, PLB+BPT > PLB+EI
[i] Pairwise comparisons: MPH+EI > PLB+EI

Table S12. Adverse events reported by parents during clinical evaluations: number of subjects that presented each adverse event at least once during treatment

	MPH + EI (N=51)	PLB+BPT (N=49)	PLB+EI (N=48)	Total (N=148)	P[a]
Mild adverse events [b]					
Decreased Appetite	33 (65%)	18 (37%)	19 (40%)	70 (47%)	0·0085 [e]
Increased appetite	0	6 (12%)	3 (6%)	9 (6%)	0·0089 [f]
Decreased weight	5 (10%)	2 (4%)	0	7 (5%)	0·070
Insomnia	17 (33%)	8 (16%)	10 (21%)	35 (24%)	0·11
Restless sleep	6 (12%)	7 (14%)	4 (8%)	17 (12%)	0·65
Drowsiness	3 (6%)	5 (10%)	5 (10%)	13 (9%)	0·72
Night awakening	3 (6%)	4 (8%)	5 (10%)	12 (8%)	0·65
Nightmares	1 (2%)	4 (8%)	4 (8%)	9 (6%)	0·33
Changes in sleeping habits during daytime	2 (4%)	1 (2%)	2 (4%)	5 (3%)	0·87
Headache	10 (20%)	8 (16%)	3 (6%)	21 (14%)	0·14
Fever	5 (10%)	2 (4%)	4 (8%)	11 (7%)	0·58
Tiredness/fatigue	2 (4%)	4 (8%)	2 (4%)	8 (5%)	0·66
Abdominal pain	8 (16%)	6 (12%)	6 (13%)	20 (14%)	0·87
Diarrhea	4 (8%)	3 (6%)	7 (15%)	14 (10%)	0·36
Constipation	4 (8%)	2 (4%)	1 (2%)	7 (5%)	0·51
Change in bowel habits (increase)	1 (2%)	1 (2%)	0	2 (1%)	1·0
Vomiting	2 (4%)	2 (4%)	6 (13%)	10 (7%)	0·18
Nausea	2 (4%)	1 (2%)	1 (2%)	4 (3%)	1·0
Cough	7 (14%)	10 (20%)	7 (15%)	24 (16%)	0·62
Runny nose	8 (16%)	8 (16%)	5 (10%)	21 (14%)	0·66
Cold symptoms	6 (12%)	4 (8%)	3 (6%)	13 (9%)	0·67
Sore throat	1 (2%)	1 (2%)	1 (2%)	3 (2%)	1·0
Rhinitis	0	1 (2%)	1 (2%)	2 (1%)	0·55
Earache	1 (2%)	0	1 (2%)	2 (1%)	0·77
Increased heart rate	4 (8%)	1 (2%)	2 (4%)	7 (5%)	0·45
Chest pain	2 (4%)	2 (4%)	0	4 (3%)	0·55
Palpitation	1 (2%)	2 (4%)	0	3 (2%)	0·54
Skin changes	3 (6%)	2 (4%)	5 (10%)	10 (7%)	0·43
Itching	2 (4%)	3 (6%)	4 (8%)	9 (6%)	0·57
Enuresis	2 (4%)	3 (6%)	2 (4%)	7 (5%)	0·90
Encopresis	2 (4%)	0	2 (4%)	4 (3%)	0·47
Tics	1 (2%)	1 (2%)	1 (2%)	3 (2%)	1·0
Stereotyped movements	0	1 (2%)	1 (2%)	2 (1%)	0·55
Pain (legs, knee or feet)	2 (4%)	2 (4%)	0	4 (3%)	0·55
Epistaxis	1 (2%)	2 (4%)	0	3 (2%)	0·54
Dry mouth	1 (2%)	1 (2%)	1 (2%)	3 (2%)	1·0
Increased thirst	1 (2%)	1 (2%)	0	2 (1%)	1·0
Increased genital manipulation	1 (2%)	1 (2%)	0	2 (1%)	1·0
Prone to crying[SEP]	12 (24%)	8 (16%)	2 (4%)	22 (15%)	0·024 [g]
Anxiety	4 (8%)	3 (6%)	3 (6%)	10 (7%)	1·0
Irritability	22 (43%)	13 (27%)	15 (31%)	50 (34%)	0·19
Aggressive behavior	9 (18%)	9 (18%)	4 (8%)	22 (15%)	0·30
Defiant behavior	8 (16%)	7 (14%)	10 (21%)	25 (17%)	0·66
Increased Hyperactivity	17 (33%)	10 (20%)	15 (31%)	42 (28%)	0·31
Increased Impulsivity	2 (4%)	0	1 (2%)	3 (2%)	0·66
Increased Inattention	0	1 (2%)	1 (2%)	2 (1%)	0·55
Sleepwalking	0	0	1 (2%)	1 (0.7%)	0·32
Stomachache	1 (2%)	0	0	1 (0.7%)	1·0
Bloated abdomen	0	0	1 (2%)	1 (0.7%)	0·32
Change in bowel habits (reduction)	0	1 (2%)	0	1 (0.7%)	0·66

Flatulence	0	1 (2%)	0	1 (0.7%)	0·66
Food poisoning	0	0	1 (2%)	1 (0.7%)	0·32
Dizziness	1 (2%)	0	0	1 (0.7%)	1·0
Increased sweating	0	0	1 (2%)	1 (0.7%)	0·32
Picking at skin or nails	1 (2%)	0	0	1 (0.7%)	1·0
Lip biting	1 (2%)	0	0	1 (0.7%)	1·0
Bites finger nails	1 (2%)	0	0	1 (0.7%)	1·0
Hair Loss	0	0	1 (2%)	1 (0.7%)	0·32
Dry Lips	1 (2%)	0	0	1 (0.7%)	1·0
Acne	1 (2%)	0	0	1 (0.7%)	1·0
Oral lesions	0	1 (2%)	0	1 (0.7%)	0·66
Diplopia	1 (2%)	0	0	1 (0.7%)	1·0
Anguish	0	0	1 (2%)	1 (0.7%)	0·32
Disengagement from activities	0	0	1 (2%)	1 (0.7%)	0·32
Euphoria	0	0	1 (2%)	1 (0.7%)	0·32
Muscle weakness (transient)	0	0	1 (2%)	1 (0.7%)	0·32
Paresthesia (transient)	1 (2%)	0	0	1 (0.7%)	1·0
Starring	1 (2%)	0	0	1 (0.7%)	1·0
Pain in forehead	1 (2%)	0	0	1 (0.7%)	1·0
Facial flush (after physical activity)	1 (2%)	0	0	1 (0.7%)	1·0
Red ears	0	0	1 (2%)	1 (0.7%)	0·32
Biting objects	1 (2%)	0	0	1 (0.7%)	1·0
Moderate adverse events [c]					
Headache	1 (2%)	4 (8%)	1 (2%)	6 (4%)	0·32
Abdominal pain	1 (2%)	2 (4%)	0	3 (2%)	0·54
Diarrhea	0	2 (4%)	1 (2%)	3 (2%)	0·32
Constipation	0	1 (2%)	0	1 (0.7%)	0·66
Vomiting	0	1 (2%)	1 (2%)	2 (1%)	0·55
Runny nose	1 (2%)	0	1 (2%)	2 (1%)	0·77
Cough	1 (2%)	0	1 (2%)	2 (1%)	0·77
Difficulty breathing	2 (4%)	0	0	2 (1%)	0·33
Pharyngitis / tonsillitis	2 (4%)	1 (2%)	1 (2%)	4 (3%)	1·0
Sinusitis	0	1 (2%)	0	1 (0.7%)	0·66
Fever	2 (4%)	3 (6%)	2 (4%)	7 (5%)	0·90
Tiredness/fatigue	0	0	1 (2%)	1 (0.7%)	0·32
Dizziness	0	0	1 (2%)	1 (0.7%)	0·32
Skin changes	1 (2%)	1 (2%)	1 (2%)	3 (2%)	1·0
Itching	0	1 (2%)	0	1 (0.7%)	0·66
Atopy	1 (2%)	0	0	1 (0.7%)	1·0
Anal bleeding	0	0	1 (2%)	1 (0.7%)	0·32
Urinary infection	0	1 (2%)	0	1 (0.7%)	0·66
Physical trauma (accidents)	1 (2%)	1 (2%)	0	2 (1%)	1·0
Severe adverse events [d]					
Asthma exacerbation	1 (2%)	0	0	1 (0.7%)	1·0
H1N1	0	1 (2%)	0	1 (0.7%)	0·66

Abbreviations: MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention.

[a] We used chi-square test of homogeneity, and multiple z-tests of two proportions with Bonferroni correction for pairwise comparisons. If more than 20% of cells have expected counts below 5. If more than 20% of cells have expected counts below 5, we used Fisher's Exact Test.

[b] Adverse events were classified as 'mild' if not required any further action.

[c] Adverse events were classified as 'moderate' if required medical evaluation or interventions (e.g., dosage adjustment or the use of an over-the-counter medication).

[d] Adverse events were classified as 'severe' if required hospitalization or represented a serious medical threat (e.g., seizure).

[e] Pairwise comparisons: MPH+EI > PLB+BPT, PLB+EI
[f] Pairwise comparisons: MPH+EI < PLB+BPT
[g] Pairwise comparisons: MPH+EI > PLB+EI, PLB+BPT > PLB+EI

Table S13. Summary of adverse events analyses [a]

	MPH+EI			PLB+BPT			PLB+EI			Time x Group Inter. p[c]	Results of Pairwise Comparison								
											MPH+EI vs. PLB+BPT			MPH+EI vs. PLB+EI			PLB+BPT vs. PLB+EI		
	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff, [b] (CI)	Baseline, mean (SE)	Week 8, mean (SE)	Mean Diff. [b] (CI)		Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]	Mean Diff. [d] (CI)	p	ES [e]
SERS [i]																			
Total Score [f]	22·95 (2·11)	18·72 (2·11)	4·22 (0·11, 8·34)	21·42 (2·12)	13·54 (2·12)	7·87 (3·82, 11·92)	20·22 (2·14)	17·44 (2·16)	2·78 (-1·34, 6·91)	0·022	5·18 (-1·89, 12·25)	0·59	0·34 (-0·12, 0·80)	1·29 (-5·86, 8·44)	0·90	0·08 (-0·38, 0·55)	-3·89 (-11·05, 3·27)	0·61	-0·25 (-0·72, 0921)
Nº of severe adv events [g]	1·00 (0·19)	0·74 (0·19)	0·26 (-0·19, 0·72)	1·05 (0·19)	0·55 (0·19)	0·50 (0·05, 0·95)	0·74 (0·19)	0·63 (0·20)	0·11 (-0·35, 0·57)	0·17	0·19 (-0·45, 0·83)	0·95	0·12 (-0·30, 0·55)	0·10 (-0·54, 0·75)	0·95	0·07 (-0·36, 0·50)	-0·08 (-0·73, 0·57)	0·95	-0·05 (-0·48, 0·38)
Insomnia [h]	2·24 (0·32)	1·84 (0·32)	0·40 (-0·36, 1·16)	1·81 (0·32)	1·43 (0·32)	0·38 (-0·38, 1·14)	2·12 (0·33)	2·02 (0·33)	0·10 (-0·67, 0·87)	0·64	0·41 (-0·66, 1·48)	0·92	0·16 (-0·25, 0·56)	-0·18 (-1·26, 0·90)	0·92	-0·07 (-0·48, 0·34)	-0·59 (-1·67, 0·49)	0·92	-0·22 (-0·63, 0·19)
Reduced Appetite [h]	1·90 (0·25)	2·85 (0·25)	-0·95 (-1·78, -0·12)	1·31 (0·25)	0·87 (0·25)	0·44 (-0·38, 1·27)	0·95 (0·26)	1·27 (0·26)	-0·32 (-1·16, 0·53)	0·0013	1·99 (1·15, 2·82)	<0·0001	0·94 (0·54, 1·33)	1·58 (0·73, 2·43)	<0·0001	0·75 (0·35, 1·15)	-0·40 (-1·25, 0·45)	0·50	-0·19 (-0·59, 0·21)
Weight [j]	21·59 (0·65)	21·32 (0·65)	0·27 (0·09, 0·45)	23·05 (0·66)	23·42 (0·66)	-0·37 (-0·55, -0·18)	20·84 (0·66)	21·32 (0·66)	-0·48 (-0·66, -0·30)	<0·0001	-2·10 (-4·30, 0·10)	0·10	-0·45 (-0·93, 0·02)	-0·005 (-2·22, 2·21)	>0·99	-0·001 (-0·48, 0·48)	2·09 (-0·12, 4·31)	0·10	0·45 (-0·03, 0·93)
Height [j]	1·13 (0·01)	1·13 (0·01)	-0·007 (-0·01, -0·002)	1·14 (0·01)	1·15 (0·01)	-0·009 (-0·01, -0·004)	1·12 (0·01)	1·13 (0·01)	-0·009 (-0·01, -0·004)	0·77	-0·02 (-0·05, 0·01)	0·52	-0·28 (-0·74, 0·19)	0·007 (-0·02, 0·04)	0·82	0·12 (-0·35, 0·59)	0·02 (-0·005, 0·05)	0·36	0·39 (-0·08, 0·86)
BMI [j]	16·95 (0·36)	16·53 (0·36)	0·42 (0·21, 0·62)	17·54 (0·36)	17·53 (0·36)	0·005 (-0·20, 0·21)	16·72 (0·36)	16·83 (0·36)	-0·11 (-0·32, 0·09)	<0·0001	-1·00 (-2·19, 0·20)	0·37	-0·39 (-0·85, 0·08)	-0·30 (-1·51, 0·91)	0·83	-0·12 (-0·59, 0·35)	0·70 (-0·51, 1·91)	0·55	0·27 (-0·20, 0·74)

Abbreviations: CI, 95% Confidence Interval; ES, Effect Size; Mean Diff, Mean Difference; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SE, Standard Error; SERS, Barkley's Side Effects Rating Scale

[a] All participants were included in an intent-to-treat analysis. Descriptive statistics reflect the estimated marginal means and proportions from Mixed Effect Models (MEM) analyses. Treatment by time interaction and pairwise comparison results are also based on estimated data from the MEM analyses.

[b] Mean difference between baseline and posttreatment.

[c] P value for treatment by time interaction term.

[d] Mean difference between groups in estimated endpoint scores

[e] Effect sizes were calculated as standardized mean differences (SMD=MD/SD pooled), where MD is the difference between means, and SD pooled is the sample-wide SD at baseline (SD pooled SERS total score = 15.40; SD pooled nº severe adv events = 1.51; SD pooled insomnia score = 2.64; SD pooled reduced appetite score = 2.12; SD pooled weight = 4.62; SD pooled height = 0.06; SD pooled imc = 2.57).

[f] Barkley's Side Effects Rating Scale (SERS) total scores range from 0 to 103, with higher scores indicating more severe adverse events.

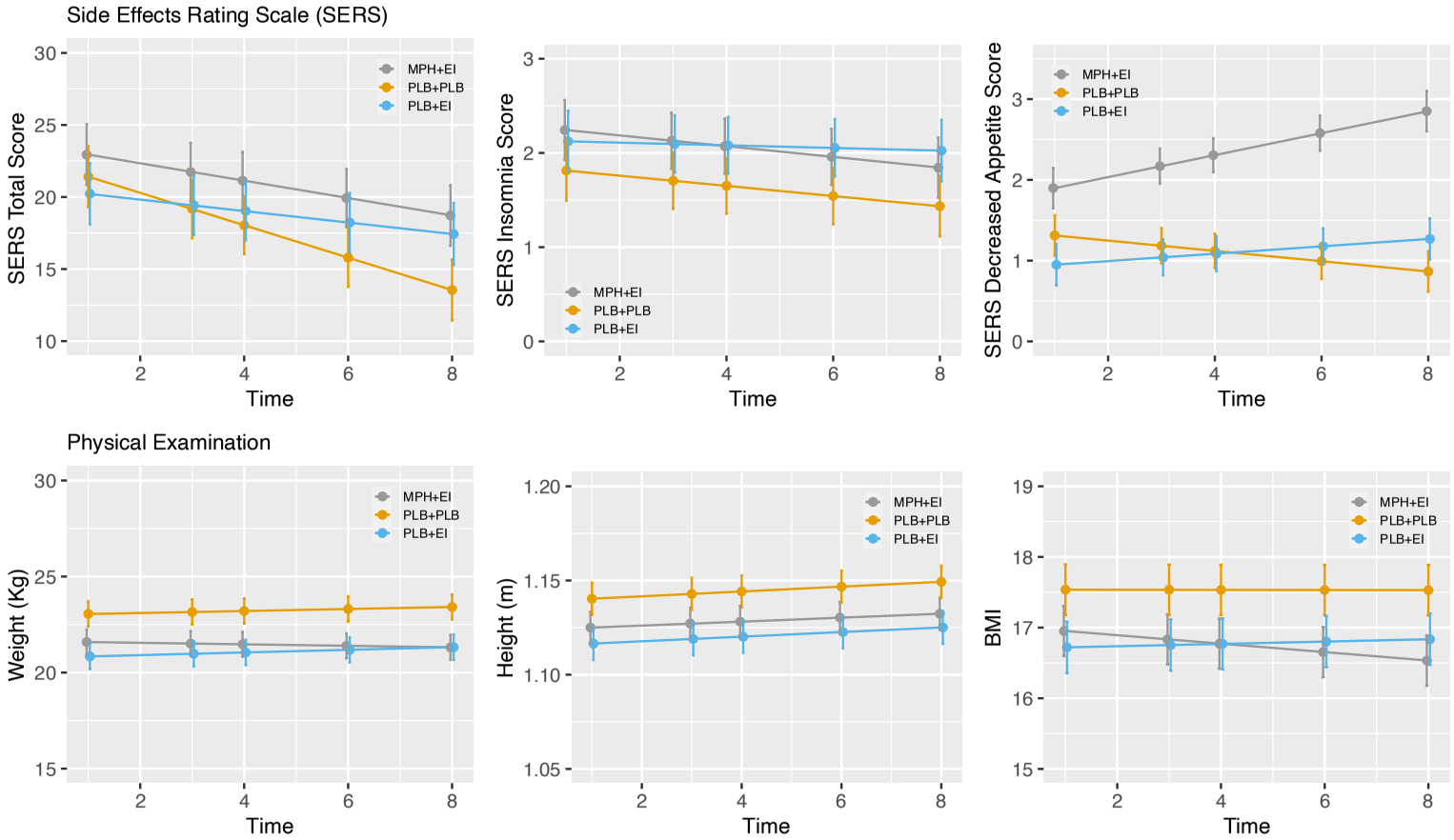
[g] Severe adverse events were defined as score ≥ 7 in the SERS. Nº of severe adv events range from 0 to 17.

[h] Barkley's Side Effects Rating Scale (SERS) insomnia scores; and SERS reduced appetite scores range from 0 to 9, with higher scores indicating more severe adverse events.

[i] n=51 MPH+EI; n=50 PLB+BPT; n=49 PLB+EI

[j] n=51 MPH+EI; n=50 PLB+BPT; n=48 PLB+EI

Figure S5. Changes in adverse events by treatment group and time



Abbreviations BMI, Body Mass Index; MPH+EI, methylphenidate + educational intervention; PLB+BPT, placebo + behavioral parenting training; PLB+EI, placebo + educational intervention; SERS, Barkley's Side Effects Rating Scale.
Estimated marginal means from Mixed Effect Models (MEM) analyses are displayed by week and treatment group. Bars indicate standard errors (SE).

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5.1.2 Discussão artigo 1

O artigo intitulado "*Efficacy and safety of methylphenidate and behavioural parent training for children aged 3–5 years with attention- deficit hyperactivity disorder: a randomised, double-blind, placebo-controlled, and sham behavioural parent training-controlled trial*" apresenta os resultados do 'Estudo Mappa', um ensaio clínico que avaliou a eficácia e segurança de metilfenidato e treinamento parental comportamental (TPC) para tratamento de crianças pré-escolares com TDAH. A descrição detalhada dos métodos e resultados, e a discussão sobre os achados e limitações do estudo foram abordadas no artigo. Aqui destaco cinco aspectos que considero significativos.

Primeiro, a relevância do estudo que teve como objetivo preencher uma importante lacuna da literatura representada pela falta de evidências científicas capazes de informar recomendações de tratamento para crianças pré-escolares com TDAH. Segundo a metodologia inovadora que avaliou o uso de metilfenidato e treinamento parental comportamental em um mesmo estudo e incluiu o uso de placebo e treinamento parental comportamental-*sham* como forma de controlar para efeitos inespecíficos dos dois tratamentos e possibilitar o cegamento dos participantes e profissionais envolvidos no estudo. Terceiro, a alta adesão das famílias aos tratamentos que reforça a robustez dos achados. Ao longo de todo o estudo, a maior parte dos participantes recebeu as intervenções conforme foram planejadas (i.e., ao menos 7 de 8 sessões de treinamento parental/intervenção educacional e ao menos 1mg/kg/d de metilfenidato ou placebo) e somente 9 indivíduos descontinuaram o tratamento. Quarto, a avaliação detalhada de eventos adversos que fornece informações úteis sobre a segurança do uso de metilfenidato no tratamento de curto-prazo de crianças pré-escolares com TDAH. Por fim, os possíveis impactos do estudo que poderão influenciar de forma significativa a prática clínica.

Apesar de suas limitações, os resultados do estudo demonstram a eficácia do uso de estimulantes na redução de sintomas de TDAH e indicam que estimulantes e treinamento parental apresentam efeitos específicos em crianças pré-escolares com TDAH. Caso sejam replicados e confirmados por meta-análises, estes achados poderão informar as diretrizes de tratamento para crianças pré-escolares com TDAH.

5.2 Artigo 2

Efficacy of stimulants for preschool attention-deficit/hyperactivity disorder: a systematic review and meta-analysis

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RESEARCH REVIEW

JCPP Advances

Efficacy of stimulants for preschool attention-deficit/hyperactivity disorder: A systematic review and meta-analysis

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Abstract

Background: Robust synthesis of evidence to support treatment recommendations for preschoolers with attention-deficit/hyperactivity disorder (ADHD) is lacking. The aim of this systematic review and meta-analysis was to review currently available evidence to evaluate the efficacy and acceptability of stimulants for preschool children with ADHD.

Methods: We searched electronic databases (CENTRAL, Embase, PubMed) from the database inception to March, 2022; and clinical trial registries through WHO ICTRP from the database inception to July, 2022, and selected double-blinded randomized controlled trials (RCTs) that compared stimulants against placebo for the treatment of preschoolers (age ≤ 7 years) with ADHD. Change in ADHD symptom severity was the primary outcome (efficacy) and all-cause dropout rates (acceptability) was the secondary outcome. Data were pooled with random-effects models weighted by the inverse of the variance. Risk of bias of individual studies were assessed with the Cochrane Risk of Bias tool version 2. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to assess the quality of evidence. This study is registered with PROSPERO (CRD42022348597).

Results: Five RCTs (three methylphenidate immediate-release, one methylphenidate extended-release, and one lisdexamfetamine) were included. The analysis of efficacy was based on 489 participants. Meta-analysis of change in ADHD symptom severity demonstrated a significant effect in favor of stimulants over placebo (standardized mean difference = −0.59; 95% CI −0.77, −0.41; $p < 0.0001$). There was no evidence of heterogeneity but some concerns about publication bias. Regardless, the confidence of evidence was considered moderate. For acceptability, stimulants did not lead to an increased rate of all-cause discontinuation rates in comparison to placebo (OR = 0.59; 95% CI 0.15, 2.37; $p = 0.45$) but the confidence of estimate was very low.

Conclusions: Our findings demonstrated that stimulants are efficacious in reducing ADHD symptoms among preschool children. Clinicians should consider the use of stimulants when making treatment recommendations for preschoolers with ADHD.

Luisa S. Sugaya and Luis C. Farhat are co-first authors of this work.

KEYWORDS
attention-deficit hyperactivity disorder, lisdexamfetamine, meta-analysis, methylphenidate, preschool, stimulants

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and/or impulsivity that typically emerge in early childhood (Posner et al., 2020). Preschool ADHD is associated with significant impairment, including peer rejection, academic underachievement, and increased risk of morbidity and mortality (Dalsgaard et al., 2015a, 2015b; Spira & Fischel, 2005). Clinical diagnosis of ADHD persists from preschool to school-age periods in approximately 90% of children (Riddle et al., 2013) and is associated with concurrent comorbidities, such as neurodevelopmental disorders, and future onset of new disorders, such as depression (Posner et al., 2020).

The prevalence of ADHD among preschoolers is estimated at 2.7%–4.3% (Vasileva et al., 2021). The clinical assessment of preschool children represents a challenge to clinicians, who must consider contextual factors, the presence of other neurodevelopmental conditions, and variations of normal development. A precise diagnosis of ADHD in preschool years represents an opportunity for early interventions, which may potentially alter the trajectory of the disorder and prevent the cascade of increasing symptoms, impairment, and comorbidity (Ruiz-Goikoetxea et al., 2018).

In the literature, there is a limited number of studies evaluating pharmacological treatments for preschoolers with ADHD. The Preschool ADHD Treatment Study (PATS) (Greenhill et al., 2006), a multi-center, multi-phase randomized controlled trial (RCT) evaluating the safety and efficacy of methylphenidate in children aged 3–5.5 years with ADHD has been considered the best evidence in the field. In the PATS, a significant improvement in ADHD symptoms was observed with methylphenidate immediate-release compared to placebo, but effect sizes were smaller and discontinuation rates were higher than previously reported in school-age children (Greenhill et al., 2006). Thus, current guidelines recommend medication for children who remain symptomatic and impaired after a trial of behavioral parent training (BPT) (Cortese, 2020). Nevertheless, meta-analyses have shown that BPT may lead to a reduction in ADHD symptoms only when outcomes are reported by unblinded parents (Rimestad et al., 2019). Also, barriers to the implementation of BPT (e.g., trained professionals' availability) may limit access to treatment. Indeed, in the US, most preschoolers with ADHD receive medications with or without psychosocial treatments; only approximately 15% receive behavioral intervention exclusively; and part of the children receive neither treatment (Visser et al., 2016).

In the past 2 years, new RCTs evaluating stimulants for preschool ADHD have been published, providing more evidence to inform the field (Childress et al., 2020, 2022; Sugaya et al., 2022). Systematic reviews and meta-analyses have supported the use of stimulants as a first-line treatment for school-aged children and adolescents (Cortese et al., 2018). However, to date, there is no meta-analysis evaluating the effects of stimulants on the treatment of preschoolers with ADHD. To fill this gap, we conducted a systematic review and meta-analysis using data from double-blind RCTs evaluating the effects of stimulants in comparison to placebo. Efficacy measured as change in ADHD symptoms was the primary outcome and acceptability measured as all-cause dropout rates was the secondary outcome. In addition, we provide a discussion integrating research findings and clinical practice.

Key points

- This is the first meta-analysis to evaluate the efficacy and acceptability of stimulants for the treatment of preschool children with attention-deficit/hyperactivity disorder (ADHD).
- Five randomized controlled trials (RCTs) were included in the analysis. Our findings demonstrated that stimulants are effective in reducing ADHD symptoms among preschoolers (standardized mean difference = −0.59; 95% CI −0.77, −0.41; $p < 0.0001$) with moderate confidence in estimates.
- Additional RCTs evaluating the short- and long-term efficacy and safety of simulants for preschool children are still a priority in the field. Future research should fill evidence gaps including the effect of these medications on functional outcomes as well potential moderators and mediators of increased/decreased effect.
- In clinical practice, stimulants should be considered by clinicians for the treatment of preschoolers with ADHD.

METHODS

Eligibility criteria

In this systematic review and meta-analysis, we included double-blinded RCTs that enrolled preschool children (age ≤ 7 years) with a primary diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-III/III-R/IV/IV-TR/5), or equivalent hyperkinetic disorder according to ICD-9/10 criteria; administered stimulants against placebo; and assessed change in ADHD symptom severity as an outcome. We did not restrict eligibility based on ADHD presentation, psychiatric or neurological comorbidities, IQ status, sex, race/ethnicity, or other sociodemographic characteristics. We included any stimulant, either methylphenidate or amphetamines, irrespective of formulation and dosages. We did not restrict eligibility based on dosing design, treatment duration, or previous/co-occurring psychotherapeutic treatments. Both parallel and crossover RCTs were eligible for inclusion. We put no restrictions on language or publication year.

We excluded studies that recruited participants who did not have a formal ADHD diagnosis or who had minimal brain dysfunction or ADHD diagnosis secondary to a genetic syndrome or perinatal exposure. We excluded studies that administered other pharmacological agents in addition to stimulants. Quasi-RCTs (e.g., use of Latin square without mention of random*; alternate days of the week) and N-of-1 trials were excluded. The protocol of the study was pre-registered in PROSPERO (CRD42022348597).

Search strategy

We searched Embase and PubMed from the database inception to March 24th, 2022, and the Cochrane Central Register of Controlled Trials and the WHO ICTRP from the database inception to July 23rd, 2022. The search terms were tailored to each database and are provided in the Supporting Information S1. We also hand-searched ClinicalTrials.gov as well as references of previous systematic reviews to look for additional studies. We emailed authors to gather unpublished data.

Study selection and data extraction

All stages of study selection and data extraction were conducted independently by a pair of researchers (LCF, PC). Any discrepancies were double-checked and resolved by discussion with another member of the review team (GVP).

Records identified through searchers in electronic databases were initially managed in EndNote to remove duplicates. Then, titles and abstracts were reviewed in Rayyan to screen potentially eligible records. The full text, supplementary materials, and other data sources were then retrieved from potentially eligible records to fully assess their eligibility and determine inclusion or exclusion. Online software was used to translate records if needed. Data from multiple reports of the same study were linked together.

We extracted summary outcome data at the study endpoint from the included RCTs. We also coded the following pieces of information: trial characteristics, including recruiting area, year study started, sponsorship (industry/non-industry), design (parallel/crossover), and number of participating centers (single/multi-center); participant characteristics, including age (range, mean [SD]), gender (proportion of boys), race (proportion of Asian-American/Black/Indian-American/White), ethnicity (proportion of Hispanics/Latinos), and diagnostic criteria; treatment characteristics, including duration, requirement of previous/concomitant psychotherapeutic interventions, medication administered, dosages (minimum, maximum, and mean). For fixed-dose RCTs which randomized participants to multiple doses of the same medication, we pooled the arms of the same medication at different doses provided that the doses were judged to be therapeutic. For crossover RCTs, we preferred pre-crossover data to avoid unit-of-analysis problems. However, most crossover RCTs do not provide pre-crossover data nor provide a comprehensive report of data to allow their inclusion appropriately, considering the within-subject design. Hence, to avoid excluding eligible studies, when pre-crossover data was not available, we extracted data from crossover RCTs as parallel RCTs.

The primary outcome was efficacy, measured as change in ADHD symptom severity. When multiple rating scales were provided, we preferred the following, in this order: the ADHD rating scale (ADHD-RS) (DuPaul, 1998) the Swanson, Nolan, and Pelham ADHD rating scale (SNAP) (Bussing et al., 2008), and the Conner's Parent/Teacher rating scales (CPRS/CTRS) (Conners et al., 1998a, 1998b). However, we also extracted data based on any other rating scales if those were the only data reported. When multiple informants were provided, we preferred the following, in this order: clinician, parent-teacher combined, teacher, and parent. Change from baseline scores was preferred over endpoint scores. Intention-to-treat (ITT) analyses were preferred, and we used the method adopted by the study to handle missing data, usually mixed model repeated measures or last observation carried forward. However, we also extracted data based on participants who completed the study (or modified ITT) if that was the only analysis reported. We extracted published standard deviations when available, but for some studies they were not reported. In those cases, we looked for 95% confidence intervals (CI), standard errors, t-values, or *p*-values which could be used to calculate standard deviations as reported in the Cochrane Handbook. We did not impute SD for any of the studies. The secondary outcome was acceptability, measured as the all-cause dropout rates. Of note, in the pre-specified protocol, we also specified our interest to examine tolerability, measured as adverse events dropout rates. However, only one study reported data for this outcome.

Data analysis

Standardized mean difference (SMD) was used as the effect size index for efficacy and odds ratio (OR) was used for acceptability. We pooled data with random-effects models weighted by the inverse of the variance. The Q-test and the I^2 statistic were used to evaluate heterogeneity. In accordance with the pre-specified protocol, we stratified analyses by compound and informants in subgroup analyses. Inferences on subgroup differences were made considering the Q-test for between subgroups heterogeneity rather than statistical significance within subgroups.

The robustness of our findings was examined in sensitivity analyses performed by excluding studies rated at high risk of bias, crossover studies without pre-crossover data, studies with less than 1 week of treatment duration, and studies that required participants to receive BPT or other psychotherapeutic intervention prior to pharmacological treatment.

For efficacy, we assessed the risk of bias of RCTs with the Cochrane tool (Sterne et al., 2019). To assess publication bias, we created funnel plots to assess asymmetry and we used the Egger regression test to evaluate small-study effects. If asymmetry was detected, we calculated adjusted effect sizes considering the trim-and-fill method. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was applied to assess the quality of evidence for efficacy and acceptability. We only considered the five factors that determine downgrading of the quality of evidence. The presence of each factor downgraded evidence one or two levels and reductions were added together to reduce the quality of evidence for the outcome.

All analyses were done in R with package *meta* (version 4.19–2) (Balduzzi et al., 2019). This study was conducted according to the Cochrane Handbook and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations. A PRISMA checklist was provided in the Supporting Information S1.

RESULTS

Study selection and characteristics

We retrieved 739 records through database search and screened 498 records after excluding duplicates. Of these, 87 records were selected for further assessment, along with 44 records identified in trial registers. Of the 131 records inspected in detail, 116 were excluded and 15 representing 5 RCTs were included (Figure 1).

The five RCTs involved 489 participants whose mean age (SD) was 4.95 (0.61) years and of which 366 (75%) were males. Most studies were conducted in the United States (3, 60%), were not sponsored by industry (3, 60%), and adopted a parallel design (4, 80%). Methylphenidate immediate-release (3, 60%), methylphenidate extended-release (1, 20%), and lisdexamfetamine (1, 20%) were the stimulants administered against placebo. Treatment trials lasted for a median of 4 weeks (IQR 2–6) (Table 1). One (20%), 2 (40%), and 2 (40%) studies were rated at high, moderate, and low risk of bias, respectively. Domain-level risk of bias assessments for each study were provided in the Supporting Information S1.

Efficacy

Meta-analysis of change in ADHD symptom severity demonstrated a significant effect in favor of stimulants over placebo (SMD = −0.59; 95% CI −0.77, −0.41; $p < 0.0001$) (Figure 2). There was no evidence of heterogeneity ($Q = 2.18$, $p = 0.70$; I^2 0%). Test for subgroups did not identify significant differences between methylphenidate versus amphetamine ($Q = 1.37$, $p = 0.24$) nor between clinician, parent-teacher combined, and parent outcomes ($Q = 1.32$, $p = 0.52$).

These findings did not change after excluding studies rated at high risk of bias (Figure S1), with less than 2 weeks of treatment duration (Figure S2), which required participants to receive psychotherapy prior to pharmacological treatment (Figure S3), and crossover studies (Figure S4).

Despite including less than 10 trials, the funnel plot indicated slight asymmetry at visual inspection (Figure S5), and the Egger regression test was significant ($t = -3.73$, $p = 0.03$). Adjusted effect sizes with the trim-and-fill method remained significant despite the addition of 2 studies (SMD = −0.52, 95% CI −0.68, −0.36, $p < 0.0001$). Still, we considered that the meta-analysis provided moderate quality of evidence for this outcome. Domain-level quality of evidence assessments were provided in the Supporting Information S1.

Acceptability

Meta-analysis of total discontinuation rates demonstrated a non-significant effect (OR = 0.59; 95% CI 0.15, 2.37; $p = 0.45$)

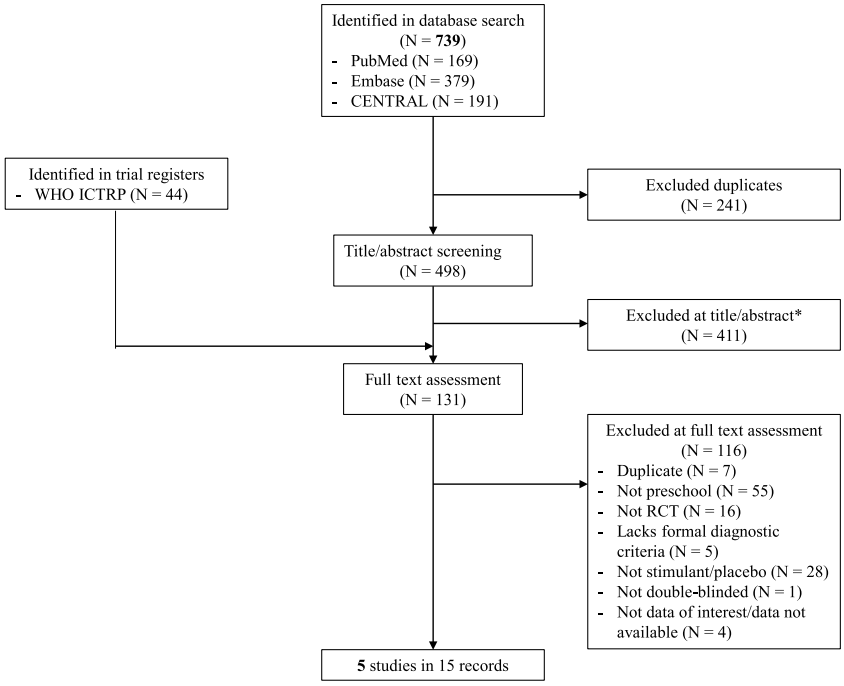

FIGURE 1 Study selection procedures.

TABLE 1 Characteristics of included studies.

	Country (year of study)	Number of participants	Age range, years (mean)	Proportion of males, %	Medication	Mean dose	Min-max dose	Dosing schedule	Treatment duration, week	Design	Instrument	Informant	Funding
Childress_2020	United States (2016)	90	4–5.7 (4.9)	76	Methylphenidate extended-release	27.5 mg/d	10–40 mg/d	Flexible	2	Parallel	ADHD-RS-IV	Clinician	Rhodes
Childress_2022	United Sates (2017)	152	4–5 (5.11)	67	Lisdexamfetamine	11.2 mg/d	10–30 mg/d	Fixed	6	Parallel	ADHD-RS-IV-PS-	Clinician	Shire
Greenhill_2006	United States (2001)	114	3–5.5 (4.76)	75	Methylphenidate immediate-release	14.2 mg/d	3.75–22.5 mg/d	Fixed	4	Parallel	SNAP-IV	Parent-teacher combined	Non-industry
Musten_1997	Canada (NR)	31	4–6 (4.84)	84	Methylphenidate immediate-release	0.8 mg/kg/d	0.6–1 mg/kg/d	Fixed	~1	Crossover	CPRS-R	Parent	Non-industry
Sugaya_2022	Brazil (2016)	153	3.9–5.9 (5.0)	83	Methylphenidate immediate-release	1.23 mg/kg/d	1.0–1.25 mg/kg/d	Flexible	8	Parallel	SNAP-IV	Parent-teacher combined	Non-industry

Abbreviation: NR, Not reported.

(Figure 3). There was evidence of heterogeneity (Q = 12.09, p = 0.002; I^2 83.5%). Test for subgroups identified significant differences between methylphenidate versus amphetamine (Q = 11.40, p = 0.0007) and a significant effect was found for methylphenidate (OR = 0.25; 95% CI 0.11, 0.54; p = 0.0005; I^2 0%), but not for amphetamines (OR = 1.88; 95% CI 0.79, 4.46; p = 0.15). We considered that the meta-analysis provided very low quality of evidence for this outcome. Domain-level quality of evidence assessments were provided in the Supporting Information S1.

DISCUSSION

This is the first meta-analysis to evaluate the efficacy and acceptability of stimulants for the treatment of preschoolers with ADHD. Five RCTs involving 489 participants were included. Results demonstrate a significant effect of stimulants compared to placebo in change of ADHD symptoms (SMD = −0.59). Despite the concern for publication bias, this finding supports the short-term efficacy of stimulants to reduce ADHD symptoms among preschoolers because the quality of evidence was considered moderate. Subgroup analyses did not identify significant differences, and the results remained the same after excluding studies at high risk of bias or with specific methodological characteristics (i.e., less than 2 weeks of treatment, requirement of psychotherapy prior to pharmacological treatment, and crossover design), indicating the robustness of the findings.

Although the effect size (SMD = −0.59) was smaller than previously reported for school-age children and adolescents (SMD = −1.02, for amphetamines, −0·78, for methylphenidate) (Cortese et al., 2018), our meta-analysis reinforces that stimulants are efficacious in the treatment of preschoolers with ADHD and may help inform treatment recommendations. These findings are particularly relevant in the context that most clinicians do not follow current treatment guidelines (Moran et al., 2019), and many preschoolers either receive medications with no evidence base or remain untreated (Danielson et al., 2017). Moreover, many barriers still limit children's access to behavioral interventions, and for many children, medication may represent a more feasible treatment.

We were unable to detect a significant effect of stimulants on all-cause discontinuation rates. On one hand, the lack of a significant effect may be related to the small number of RCTs available, particularly considering the relatively low event rates that were observed in the included RCTs. On the other hand, the lack of a significant effect may be related to pooling studies with different dosing designs. In a recent systematic review and meta-analyses, we showed that dose escalation adopted in flexible-dose studies increases acceptability of medications, while the same association is not found in fixed-dose studies which administer random doses to participants without considering their individual benefit-to-risk ratio of higher doses (Farhat et al., 2022). Indeed, in our analyses flexible-dose studies (Childress et al., 2020; Sugaya et al., 2022) demonstrated increased acceptability whereas the fixed-dose studies (Childress et al., 2022; Greenhill et al., 2006; Musten et al., 1997) demonstrated decreased acceptability. Regardless, because there are few studies available, we opted to consider the pooled evidence and downgrade the quality of evidence due to imprecision rather than focus on the subgroup analysis to avoid overinterpreting findings at this stage.

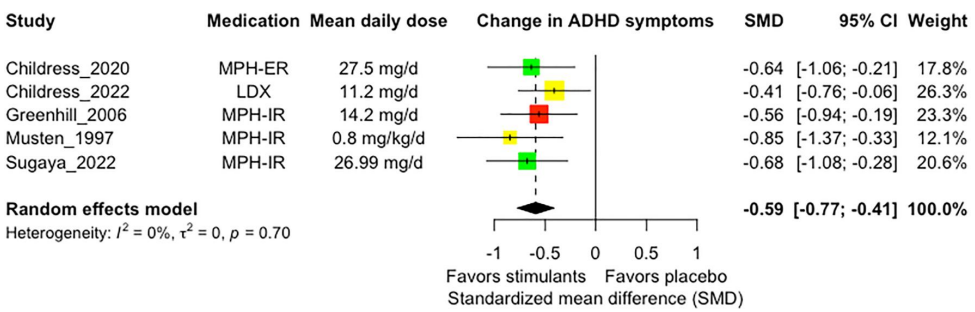

FIGURE 2 Forest plot for change in ADHD symptom severity. Risk of bias: green, low risk; yellow, some concern; red, high risk. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; LDX, lisdexamfetamine; MPH-ER, methylphenidate extended-release; MPH-IR, methylphenidate immediate-release; SMD, standardized mean difference.

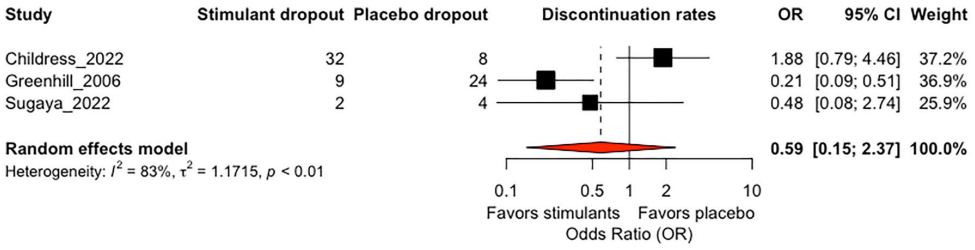

FIGURE 3 Forest plot for discontinuation rate.

Due to the lack of data on adverse event dropout rates, it was not possible to examine stimulants' tolerability. However, results from the individual RCTs indicate that stimulants are generally safe in the short-term for the treatment of preschoolers with ADHD. Across studies, only one serious adverse event was judged to be related to medication (i.e., a possible seizure), as described by the PATS study (Wigal et al., 2006). Most adverse events reported by the RCTs were considered mild or moderate. In all studies, except for Musten et al. (1997) (Musten et al., 1997)—which did not describe the occurrence of specific adverse events—decreased appetite, irritability, and insomnia were reported among the most frequent adverse events. Decrease in bodyweight/BMI was reported by 4 RCTs, but severe weight loss was only reported for 3 children in the PATS study. Severe insomnia was reported by 8 children, 6 of them in the PATS. Specifically, irritability/affect lability may be clinically relevant adverse events that may occur more frequently among preschoolers than in school-aged children. It was reported as the reason for discontinuation by 9 of 14 children in the PATS study open-label lead-in phase (Greenhill et al., 2006) and by 3 of 8 children in the study conducted by Childress et al. (2022) (Childress et al., 2022). On the other hand, anxiety was reported in 2 studies, and severe anxiety was reported once in the PATS study (Wigal et al., 2006).

Other adverse events may warrant some attention because of potential long-term concerns. First, increase in heart rate and blood pressure was observed across studies, except for Musten et al. (1997) (Musten et al., 1997). In the PATS study (Wigal et al., 2006) and in the MAPPA study (Sugaya et al., 2022), there was no significant difference between children using stimulants or placebo. However, Childress et al. (2020) (Childress et al., 2020) described 3 cases of hypertension and 1 case of tachycardia as possibly or probably related to the use of medication. It is possible that children exposed to stimulants at an early age may develop cardiovascular adverse events in the long-term, for example, increased heart rate. It is important to consider that drug exposure may have different effects across developmental maturation stages. However, for individuals who started using stimulants during school-age years, only mild increases in heart rate have been documented and there was no evidence of increased risk of hypertension over a 10-year period (Vitiello et al., 2012). Also, a meta-analysis of observational studies did not show a significant association between medications for ADHD and serious cardiovascular events such as stroke, myocardial infarction, or death from any cause, although a modest increase in the risk of sudden death/arrythmia were not ruled-out (Liu et al., 2019). Second, the PATS study—the only that included a 10-month open-label maintenance phase—found decrements in growth rates in preschoolers on medication compared to placebo (Swanson et al., 2006). Evidence suggests that stimulants effect on height may be moderated by the level of stimulant exposure and may be attenuated by treatment discontinuation (Greenhill et al., 2020). However, more studies focusing on long-term implications of stimulants for preschool ADHD are necessary to provide a clearer understanding of the potential hazards of stimulant use in this population.

Our study has some limitations. First, only 5 RTCs were identified (one with lisdexamfetamine, one with methylphenidate extended-release, and three with methylphenidate immediate-release). We were underpowered to detect significant differences in dichotomous outcomes and subgroup analyses. Hence, negative findings for subgroup analyses have to be interpreted with caution. Second, our analyses pooled data from multiple informants (i.e., parents, parent-teachers, and clinicians). Although we were unable to detect significant differences across informants, future meta-analyses should

consider evaluating data from each informant separately as more RCTs become available. Third, due to the lack of data, it was not possible to examine stimulants' tolerability or the occurrence of specific adverse events. Fourth, we cannot discard the presence of publication bias. Although the funnel plot and Egger regression test are traditionally done with 10 or more studies, they have been previously used in meta-analysis with 5 studies (Zhou et al., 2021). We opted to use these methods to provide the readership some visual evidence of publication bias. The findings should be interpreted with caution, but, irrespective of the limited number of RCTs, we detected a slight asymmetry in the funnel plot and the Egger regression test was significant. Regardless of statistical tests, we also note that there has been a recent increased interest in the effects of stimulants for preschoolers, with 3 of the 5 studies published in the last 3 years (Childress et al., 2020, 2022; Sugaya et al., 2022). Some of these studies also adopted a design that may maximize efficacy. For instance, the PATS (Greenhill et al., 2006) and Childress et al. (2020) (Childress et al., 2020) studies have multiple steps which may contribute to self-selection of participants who experience the most benefit with the medication. Additional studies are required to corroborate the findings from the ones that have been included in this review. Nevertheless, the confidence of the estimate was still judged at moderate. Fifth, most studies were conducted in North America (i.e., United States and Canada), and only one study was conducted in a low-middle income country (i.e., Brazil), limiting the generalizability of the findings to developing countries. Sixth, our analyses were restricted to stimulants' effect on ADHD symptoms and did not evaluate functional outcomes. Finally, treatment duration ranged from 1 to 8 weeks and no inference can be made about the long-term effect and acceptability of stimulants for preschoolers.

CONCLUSION

In conclusion, our meta-analysis demonstrated stimulants' efficacy in reducing ADHD symptoms among preschoolers, with moderate quality of evidence. For acceptability, stimulants did not lead to an increased rate of all-cause discontinuation rates in comparison to placebo, with very low quality of confidence on evidence. These results should be considered by clinicians when making treatment recommendations. In clinical practice, adverse events should be monitored and balanced against medication benefits.

Additional RCTs evaluating the short- and long-term efficacy and safety of simulants for preschool children are still a priority in the field. Specifically, more studies evaluating long-acting formulations of methylphenidate and amphetamines are needed. Furthermore, there is also a need for more studies that do not adopt an enrichment design, that is, select participants who were responders in an initial open-label phase, because this design may artificially increase the effect size in favor of the medication. Future RCTs may also evaluate stimulants as first-line intervention (i.e., without requiring prior/concomitant psychotherapy), and a flexible dosing titration may increase tolerability. Detailed reports of adverse events, including measures of blood pressure, pulse, bodyweight, and height are important, especially over longer periods of time. Future research should also fill evidence gaps including the effect of these medications on functional outcomes (e.g., school readiness, global functioning) as well potential moderators and mediators of increased/decreased effect.

PRACTICAL GUIDANCE: CLINICAL RECOMMENDATIONS

Assessment

Accurate diagnosis is essential and clinical assessment of preschoolers can be challenging. A discussion on this topic is beyond the scope of this review. The assessment of preschool children must include a comprehensive multi-informant, multi-method approach that takes into account not only current behavioral concerns, but all domains of development, home and school environment, and the level and nature of the impairment. Also, the assessment of personal and family history of cardiac diseases, and complete medical evaluation are necessary. Physical examination should include measures of height, weight, blood pressure, and pulse. Consultation from specialists (e.g., cardiologists), and complementary exams (e.g., electrocardiogram) are not routinely needed and should be required based on an individualized evaluation.

Treatment planning

For school-age children and adolescents with ADHD, there are numerous RCTs evaluating the effect of stimulants. Meta-analysis demonstrated the efficacy of both methylphenidate and amphetamines. However, amphetamines increased diastolic blood pressure and were less well tolerated than placebo, while methylphenidate had better acceptability than placebo. Thus, methylphenidate has been suggested as the first-line pharmacological treatment (Cortese et al., 2018).

In contrast, we found only 5 double-blind RCTs evaluating the effect of stimulants for preschoolers with ADHD. The meta-analysis demonstrated stimulants' efficacy in reducing ADHD symptoms. However, analyses were underpowered to detect significant differences in the effect of methylphenidate and amphetamines. Conversely, subgroup analyses identified differences between methylphenidate and amphetamine for acceptability, but the quality of evidence was considered very-low. Therefore, treatment planning for preschool children with ADHD should consider both the findings and limitations of the study.

In this context, honest communication and a shared decision between clinicians and parents are recommended. Individual treatment plans should initiate with education of families and teachers, context modification and accommodations, and take into account symptom severity, functional impairment, presence of comorbidities, dysfunctional parenting practices, treatment availability, and family preferences. Discussion with families should consider both treatments' risks and benefits, and the negative consequences of ADHD.

Currently, guidelines recommend psychosocial interventions as first-line treatment for preschoolers with ADHD (Cortese, 2020). However, availability of evidence-based therapies is very limited across the world, especially in settings with limited resources. Also, meta-analysis does not support the efficacy of BPT in reducing ADHD symptoms when outcomes were rated by blinded evaluators

(Rimestad et al., 2019). In the MAPPA study (Sugaya et al., 2022), a multi-arm, randomized, double-blind, placebo- and sham BPT-controlled clinical trial comparing methylphenidate and BPT over a control group, BPT had no significant effect over reduction of symptoms in comparison to control group, despite an effect size of −0.44 (95% CI −0.89, 0.003), and produced an improved global functioning. In addition, most guidelines were published before 2020 and, at that point, there were only 2 double-blind RCTs evaluating the use of stimulants for preschoolers with ADHD (Greenhill et al., 2006; Musten et al., 1997). Since then, 3 additional double-blind RCTs were published showing stimulants' efficacy in reducing ADHD symptoms when compared to placebo (Childress et al., 2020, 2022; Sugaya et al., 2022) and current meta-analysis supports the efficacy of stimulants with moderate quality of evidence.

Thus, we argue that BPT must be indicated particularly for parents whose children present comorbid oppositional defiant disorder or conduct problems (Groenman et al., 2021), or for parents who display significant dysfunctional practices to manage their children's behavior (Rimestad et al., 2019), and in settings where parents can have access to it. Stimulants should also be considered without the requirement of a previous trial of BPT for treatment of preschoolers with ADHD especially for children >4 years of age with moderate or severe symptoms; when there is limited access to BPT; and when the pharmacological treatment is the family preference. Considering that most RCTs evaluated the use of methylphenidate immediate-release, it may be the medication of choice. Long-acting methylphenidate formulation and lisdexamfetamine can also be considered. A slow titration regimen with frequent re-assessments is recommended to optimize treatment and improve tolerability. Treatment monitoring should include a systematic assessment of symptoms, functional impairment, and adverse events including decreased appetite, irritability, and insomnia, as well as measures of height, bodyweight, pulse, and blood pressure. Trials of discontinuation should be actively considered and discussed with families, especially if there is remission of symptoms over 6–12 months of follow-up.

To date, there is no clinical trial evaluating the combination of stimulants and behavioral interventions for preschoolers with ADHD. It is hypothesized that these two treatments have different mechanisms and could be used to target different areas of impairment. In the MAPPA study (Sugaya et al., 2022), secondary outcome analyses showed that methylphenidate was associated with improvement in cognitive measures of attention while BPT was associated with improvement in irritability. Therefore, specific groups may particularly benefit from a multimodal approach as reported by the Multimodal Treatment of ADHD Study (MTA). In the MTA, school-age children with comorbid anxiety and disruptive behavior disorder had a greater response to the combined treatment (Jensen et al., 2001). Future studies with preschoolers evaluating the efficacy of combined treatment will be important to guide treatment recommendations.

For children that do not tolerate the use of stimulants, alpha-agonists could be considered with caution. Indeed, alpha-agonists have been commonly used among this population, both in isolation or in combination with stimulants (Panther et al., 2017). However, clinicians should take into account that there is no double-blind RCT evaluating the use of alpha-agonists for preschool children with ADHD, and its use has been supported by case reports (Lee, 1997) and a retrospective chart review (Harstad et al., 2021). Based on data from studies conducted with older children, prior to the use of alpha-agonists, clinicians should assess the occurrence of symptoms of hypotension (e.g., dizziness), cardiac conditions, and family history of QTc prolongation. Electrocardiogram and consultation from specialists should be considered for specific individuals (Hirota et al., 2014). To date, there is only one double-blind RCT that compared atomoxetine and placebo for the treatment of children aged 5–6 years (Kratochvil et al., 2011). Although results showed a reduction of ADHD symptoms, most children remained moderately to severely ill at the completion of the study, and they were more likely to have decreased appetite, gastrointestinal upset, and sedation.

Antipsychotics are widely prescribed for young children across the globe (Sultan et al., 2019) but current evidence does not support ADHD as an indication. There is one small double-blind RCT comparing risperidone and methylphenidate for children with 3–6 years, with no difference in response between groups (Arabgol et al., 2015). The long-term metabolic adverse events that have already been associated with the use of antipsychotics, including weight gain, hyperlipidemia, diabetes, and negative impact on bone metabolism are concerning (Correll, 2009). One exception are school-age children with ADHD and comorbid disruptive behavior disorders or severe aggressiveness. Studies with this population showed that adding risperidone, after behavioral intervention and stimulant optimization, reduced aggressiveness, ADHD, and ODD symptoms (Blader et al., 2021). Importantly, before adding a second medication targeting disruptive behaviors, it is fundamental to optimize the stimulant dose (Blader et al., 2021).

Irrespective of the chosen treatment, clinicians should be aware that there is limited evidence regarding the risks and benefits of long-term treatment. Thus, careful and continuous clinical assessment of symptoms, global functioning, and adverse events is mandatory, as well as periodic revision of diagnosis, new arising comorbidities and family environment. In the future, rigorous RCTs with long-term follow-up and the identification of clinical predictors of response and adverse events may be helpful to guide treatment decisions.

AUTHOR CONTRIBUTIONS

Luisa S. Sugaya: Conceptualization; Writing – original draft; Writing – review and editing. **Luis C. Farhat:** Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review and editing. **Pietro Califano:** Data curation; Writing – review and editing. **Guilherme V. Polanczyk:** Conceptualization; Funding acquisition; Methodology; Supervision; Writing – original draft; Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

GVP, in the last 3 years, has been a consultant, member of advisory board, and/or speaker for Aché, Abbott, Medice, Novo Nordisk, and Takeda; he has received royalties from Editora Manole. He is also a Joint Editor for JCPP *Advances*. The remaining authors have declared they have no potential or competing conflicts of interest.

OPEN RESEARCH BADGES

This article has been awarded <Open Data, Open Material, Preregistered> badges. All materials and data are publicly accessible via the Open Science Framework at (https://osf.io/98wxt/). Learn more about the Open Practices badges from the Center for Open Science: https://osf.io/tvyxz/wiki

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available at https://osf.io/98wxt/.

ETHICAL CONSIDERATIONS

An ethics statement is not applicable to this paper.

PROTOCOL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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5.2.1 Artigo 2: material suplementar

Supporting Information

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	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	pp 9-10
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	pp 9,11
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p 10
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	pp 9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	pp 10-11

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p 11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	pp 10-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p 10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p 11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p 11
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p 11
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	pp 11-12
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	pp 11-12
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supp 7-9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supp 12-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	pp 12-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	pp 12-13
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	pp 12-13
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	pp 12- 13
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	pp 12- 13
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pp 13-16

Section and Topic	Item #	Checklist item	Location where item is reported
	23b	Discuss any limitations of the evidence included in the review.	pp 14-16
	23c	Discuss any limitations of the review processes used.	pp 15-16
	23d	Discuss implications of the results for practice, policy, and future research.	pp 17-18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p 8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p 8
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	p 10
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p 1
Competing interests	26	Declare any competing interests of review authors.	p 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p 1

SEARCH STRATEGY

PubMed

("Attention Deficit Disorder with Hyperactivity"[Mesh] OR adhd[tiab] OR "attention deficit*"[tiab]) AND ("Methylphenidate"[Mesh] OR "Dexmethylphenidate"[Mesh] OR Focalin[tiab] OR Dexmethylphenidate[tiab] OR Methylphenidate[tiab] OR Biphentin[tiab] OR Concerta[tiab] OR Daytrana[tiab] OR Methylphenidate[tiab] OR Equasym[tiab] OR Methylin[tiab] OR Ritalin*[tiab] OR Medikinet[tiab] OR Metadate[tiab] OR Quillivant[tiab] OR "Amphetamines"[Mesh] OR Adderall[tiab] OR Amphetamine[tiab] OR Amfetamine[tiab] OR Dexamfetamine[tiab] OR Dexamphetamine[tiab] OR Dexedrine[tiab] OR Dextroamphetamine[tiab] OR DextroStat[tiab] OR Elvanse[tiab] OR Lisdexamfetamine[tiab] OR Vyvanse[tiab]) AND (preschool* OR toddler*) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])

Embase

("Attention Deficit Disorder with Hyperactivity" OR adhd OR "attention deficit*") AND ("Methylphenidate" OR "Dexmethylphenidate" OR Focalin OR Dexmethylphenidate OR Methylphenidate OR Biphentin OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Ritalin* OR Medikinet OR Metadate OR Quillivant OR "Amphetamines" OR Adderall OR Amphetamine OR Amfetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Elvanse OR Lisdexamfetamine OR Vyvanse) AND (preschool* OR toddler*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial) NOT (animals NOT humans)

CENTRAL

(("Attention Deficit Disorder with Hyperactivity" OR adhd OR "attention deficit*")) AND (("Methylphenidate" OR "Dexmethylphenidate" OR Focalin OR Dexmethylphenidate OR Methylphenidate OR Biphentin OR Concerta OR Daytrana OR Methylphenidate OR Equasym OR Methylin OR Ritalin* OR Medikinet OR Metadate OR Quillivant OR "Amphetamines" OR Adderall OR Amphetamine OR Amfetamine OR Dexamfetamine OR Dexamphetamine OR Dexedrine OR Dextroamphetamine OR DextroStat OR Elvanse OR Lisdexamfetamine OR Vyvanse)) AND ((preschool* OR toddler*)) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial)):ti,ab,kw

WHO ICTRP

("Attention Deficit Disorder with Hyperactivity" OR adhd OR "attention deficit*") AND (preschool* OR toddler*)

DOMAIN-LEVEL RISK OF BIAS ASSESSMENT FOR EACH STUDY

Childress_2020

Domain	Judgment	Justification
Randomisation process	Low	"Children were randomized in a 1:1 ratio through a computer-generated randomization schedule to either continue their optimized dose or receive matching placebo" (Journal article, page 60). There are no specific pieces of information about how allocation sequence was concealed during the study. However, the investigator confirmed sites were not aware of the sequence (correspondence through email) Baseline characteristics were relatively similar across treatment groups. (Journal article, Table 1)
Deviations from interventions	Low	A matching placebo was used. There are no specific pieces of information about blinding of therapists. However, the investigator confirmed site personnel did not know what treatments subjects received (correspondence through email). "Several populations were defined for purposes of data analysis: (3) ITT-efficacy evaluable (ITT-E) population, including all children in the ITT population who completed ADHD-RS-IV assessments at the end of the open-label Phase 4 (DB phase baseline) and had at least one postbaseline ADHD-RS-IV assessment" (journal article, page 61)
Missing outcome data	Low	Only 4 participants discontinued the study during the double-blinded phase. (Journal article, Figure 2)
Outcome measurement	Low	There are no specific pieces of information about blinding of investigators/outcome assessors. However, the investigator confirmed site personnel did not know what treatments subjects received (correspondence through email)
Outcome selection	Low	"The primary efficacy measure is the comparison of the two treatment groups (optimized dose vs placebo) using the change in ADHD-RS-IV Total Score during the double-blind phase, i.e., the change from end of open label phase to end of double-blind phase" (protocol, available in ClinicalTrials.gov)

Childress_2022

Domain	Judgment	Justification
Randomisation process	Low	"In this double-blind study, treatment assignments were determined using a randomization schedule, with each treatment assigned by an interactive Web response system (IWRS)" (Journal article, page 3). Baseline characteristics were relatively similar across treatment groups. (Journal article, Table 1)
Deviations from interventions	Low	"To protect study blinding, LDX and PBO capsules appeared identical" (journal article, page 3).

		There were numerous protocol deviations, however analyses followed a modified intent-to-treat principle: "Statistical analysis of efficacy compared the pooled LDX doses (i.e., the 10-,20-, and 30-mg doses) with PBO, and included all randomized participants receiving ≥ 1 dose of LDX and having ≥ 1 postbaseline ADHD-RS-IV-PS-TS assessment". Participants from the 5 mg arm were excluded from efficacy analysis, but this was pre-specified in the statistical analysis plan "Specifically, these analyses will compare placebo and pooled SPD489 10, 20, 30 mg dose strengths together, excluding the 5 mg arm" (statistical analysis plan, page 26, available in ClinicalTrials.gov)
Missing outcome data	Some concerns	There were some discontinuations (40, 25%) and those were relatively imbalanced across treatment arms (PBO 8, 17%; LDX 32, 28%). However, discontinuations due to adverse events were relatively balanced across groups (PBO 2, 4%; LDX 5%).
Outcome measurement	Low	Investigators were blinded to treatment assignments.
Outcome selection	Low	"The primary efficacy endpoint is defined as the change from baseline in clinician-administered ADHD-RS-IV Preschool Version Total Score at Visit 6 (Week 6)" (statistical analysis plan, page 26).

Greenhill_2006

Domain	Judgment	Justification
Randomisation process	Low	"Randomization was done centrally at the coordinating site using a computerized stratified randomization, 1:1:1:1 starting dose allocation ratio, using a randomized, balanced, crossover protocol designed to avoid order effects. A second randomization to active MPH or to placebo was performed before entering the parallel-design, placebo-controlled phase" (Journal article, page 1286)
Deviations from interventions	Low	"Except in emergencies, clinicians remained blind to the dose sequences." (Journal article, page 1286). "Subjects were randomized to one of five sequences of four different MPH doses (1.25, 2.5, 5, 7.5 mg) and placebo administered t.i.d. in identical capsules for 1 week each" (Journal article, page 1286). "All analyses were run using the intent-to-treat principle (i.e., each observation obtained for the child was used in the analysis including those from children who entered each of the two phases under consideration and did not complete the phase".
Missing outcome data	High	There were considerable discontinuations (36, 32%) and those were imbalanced across treatment arms (PBO 24, 45%; MPH 9, 15%)
Outcome measurement	Low	Parents and teachers were blinded to treatment assignment
Outcome selection	Some concerns	Change in ADHD symptoms considering the primary efficacy

		composite SNAP as a continuous measure was a *post hoc* analysis. "In an additional post hoc, intent-to-treat, last observation carried forward analysis, we used the primary efficacy composite SNAP rating of the parallel phase as a continuous measure to supplement the categorical approach cited above". (Journal article, page 1290).

Musten_1997

Domain	Judgment	Justification
Randomisation process	Low	"Treatment was presented in a fully randomized order prepared by the hospital's pharmacy department" (Journal article, page 1408).
Deviations from interventions	Low	"Two doses (0.3 mg/kg and 0.5 mg/kg) of MPH and a lactose placebo were prepared by the pharmacy at the Children's Hospital of Eastern Ontario to the nearest 2.5 mg and placed in orange gelatin capsules (size 16, Ely Lilly Company) to disguise the taste differences between placebo and the two doses." (Journal article, page 1408) "all subjects, research personnel, and medical personnel were unaware of the order" (Journal article, page 1408)
Missing outcome data	Some concerns	"A final total of 41 children participated in the medication phase after parents received feedback and gave informed consent for medication. Of these, 31 children completed the treatment regimen, 4 children withdrew from treatment, and 6 children did not have completed assessment protocols (questionnaires) after one or all of the treatment phases".
Outcome measurement	Low	Parents were blinded to treatment.
Outcome selection	Low	We were unable to locate a protocol. However, the CPRS was used, and the hyperactivity index was reported – those procedures were considered expected in the field at the time of the study.

Sugaya et al., 2022

Domain	Judgment	Justification
Randomisation process	Low	"The randomization scheme was generated by an independent research manager with experience in the execution of clinical trials and no involvement in this trial using a permuted block randomization procedure with equal allocation and 5 blocks with N = 30 (https://www.randomization.com). Three additional participants that had initiated the pre-trial assessment before the inclusion of the 150th participant were considered eligible and were randomized. For their inclusion, an identical randomization scheme was generated, except that the block size was 3." (Supporting file, page 3)
Deviations from interventions	Low	"Parents, teachers, child and adolescent psychiatrists that conducted child's initial assessment and clinical evaluations during the trial, research assistants, and independent evaluators remained fully blinded. Only the study pharmacist was unblinded to medication treatment" (Supporting file, page 3)

		"Placebo was corn flour only, encapsulated in capsules identical to the MPH in color, size, and weight." (Journal article, page 9)
Missing outcome data	Low	There were few discontinuation rates in the study.
Outcome measurement	Low	"The first primary outcome was ADHD symptoms measured by the SNAP-IV scale, which was rated by a blinded independent evaluator based on parental interview and completed independently by teachers who were also blinded to treatment conditions" (Journal article, page 11)
Outcome selection	Low	The SNAP was the primary efficacy endpoint in ClinicalTrials.gov

SUPPLEMENTARY FIGURES

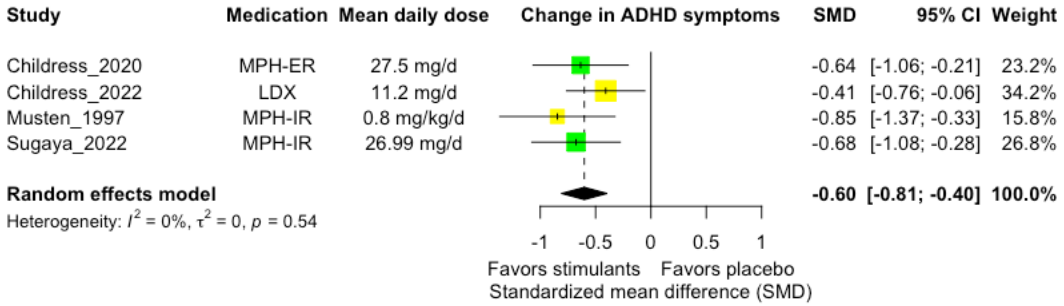

Figure S1. Forest plot for efficacy in sensitivity analysis excluding studies rated at high risk of bias.
LDX, lisdexamfetamine; MPH-ER, methylphenidate Extended-release; MPH-IR, methylphenidate immediate-release; SMD, standardized mean difference. Risk of bias: green, low risk; yellow, some concern.

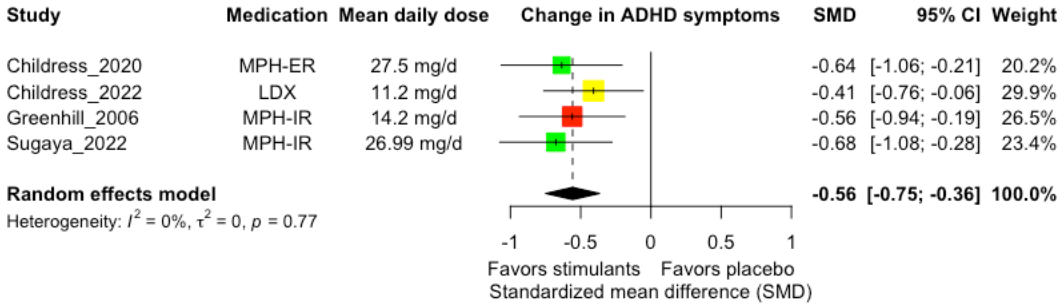

Figure S2. Forest plot for efficacy in sensitivity analysis excluding studies which lasted for less than 2 weeks.
LDX, lisdexamfetamine; MPH-ER, methylphenidate Extended-release; MPH-IR, methylphenidate immediate-release; SMD, standardized mean difference. Risk of bias: green, low risk; yellow, some concern; red, high risk

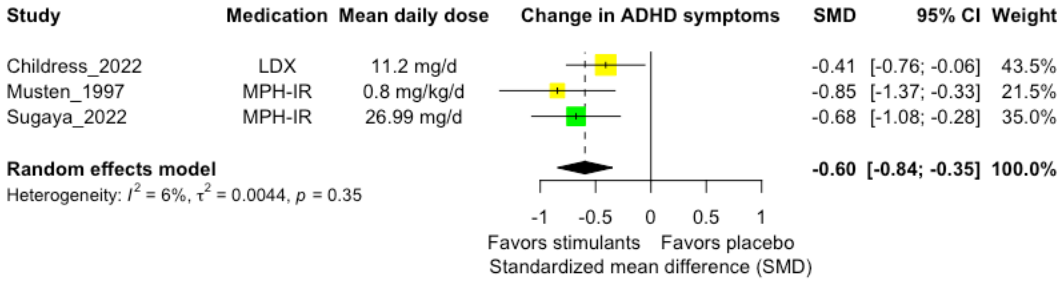

Figure S3. Forest plot for efficacy in sensitivity analysis excluding studies which required participants to receive psychotherapy prior to pharmacological treatment.
LDX, lisdexamfetamine; MPH-IR, methylphenidate immediate-release; SMD, standardized mean difference Risk of bias: green, low risk; yellow, some concern.

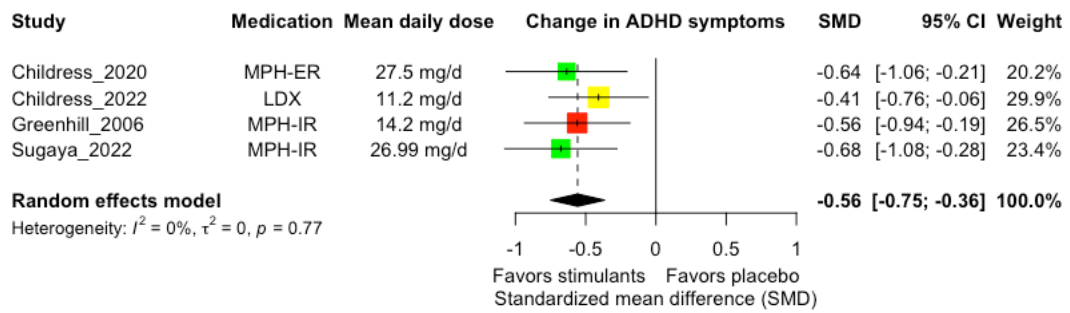

Figure S4. Forest plot for efficacy in sensitivity analysis excluding crossover studies.
LDX, lisdexamfetamine; MPH-ER, methylphenidate Extended-release; MPH-IR, methylphenidate immediate-release; SMD, standardized mean difference. Risk of bias: green, low risk; yellow, some concern; red, high risk

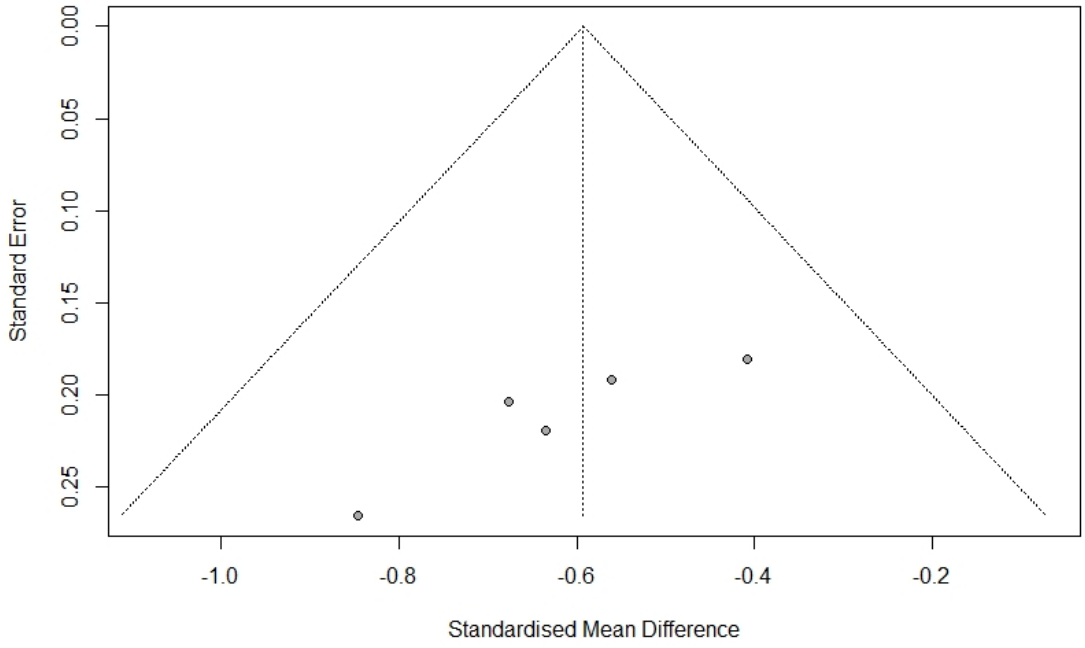

Figure S5. Funnel plot for efficacy

DOMAIN-LEVEL QUALITY OF EVIDENCE ASSESSMENT FOR EACH OUTCOME

Efficacy

Domain	Judgment	Justification
Study limitations	No serious limitation, do not downgrade	Most information came from studies at low or at some concerns of risk of bias. Therefore, we considered that potential limitations were unlikely to lower confidence in the estimate of effect following recommendations from GRADE.
Inconsistency	No serious limitation, do not downgrade	There was no evidence of statistical heterogeneity. Visual inspection of funnel plots did not indicate considerable between-study variability.
Imprecision	No serious limitation, do not downgrade	Considering α 0.05, β 0.2, a mean difference between treatment groups 5.94, a standard deviation of 10.62 and one-sided type I error, the calculated sample size was 82 (41 in each treatment group). Hence, our meta-analysis was powered to detect a Cohen d of 0.56. Additionally, the 95% confidence interval does not overlap with the null effect.
Indirectness	No serious limitation, do not downgrade	Our strict eligibility criteria ensured our population was directly relevant to our research question (individuals in preschool with DSM ADHD). Two studies (Childress_2020, Greenhill_2006) individuals were responders to the medication that was administered in the RDBCT, which may limit generalizability. However, we opted not to downgrade the quality of evidence because most studies information came from studies in which individuals were not originally considered responders.
Publication bias	Serious limitation, downgraded one level	We opted to downgrade one level quality of evidence due to publication bias. There was statistical evidence of publication bias and funnel plot asymmetry. Besides, most studies have been relatively recent, and early publications

		may be more likely to report positive results.

Acceptability

Domain	Judgment	Justification
Study limitations	No serious limitation, do not downgrade	We opted not to downgrade quality of evidence because discontinuation rates are directly related to risk of bias assessments (missing outcome data).
Inconsistency	Serious limitation, downgraded one level	There was evidence of statistical inconsistency. Subgroup analysis stratified by compound was able to resolve heterogeneity, likely because it separated fixed-dose and flexible-dose studies. Yet, because subgroup analyses may be spurious, particularly with so few studies, we opted not to use the subgroup analysis and downgrade quality of evidence one level.
Imprecision	Very serious limitation, downgraded two levels	We had a small sample size and were underpowered to detect differences in dichotomous outcomes. Additionally, the 95% CI of our estimate crossed the threshold for null effect while also excluding important benefit AND important harm (0.8, 1.25)
Indirectness	Serious limitation, downgraded one level	
Publication bias	No serious limitation, do not downgrade	We opted not to downgrade quality of evidence. Although it is possible that studies with high discontinuation rates would not be published, at the same time dropout rates are not typical outcomes in RDBCTs and therefore may be less influenced by editorial preferences.

5.2.2 Discussão artigo 2

O artigo intitulado *"Efficacy of stimulants for preschool attention-deficit/hyperactivity disorder: a systematic review and meta-analysis"* foi a primeira meta-análise a avaliar a eficácia e a aceitabilidade de estimulantes para tratamento de crianças em pré-escolares com TDAH. Além disso, a discussão deste artigo também teve o objetivo fornecer uma revisão abrangente e atualizada sobre o tratamento farmacológico de pré-escolares com TDAH.

No total, foram incluídos cinco ensaios clínicos randomizados duplo-cegos, controlados por placebo avaliando a o uso de estimulantes (três com metilfenidato liberação-imediata, um com metilfenidato liberação-prolongada, e um com lisdexanfetamina). A meta-análise demonstrou que o uso de estimulantes é eficaz para redução de sintomas de TDAH, com confiabilidade da evidência moderada. Estes resultados corroboram os resultados encontrados no 'Estudo Mappa' (artigo 1) e suportam o uso de estimulantes para tratamento de pré-escolares com TDAH, contribuindo assim para a discussão sobre as recomendações de tratamento para esta população.

No entanto, é importante considerar que a qualidade da evidência sobre aceitabilidade foi considerada muito baixa, e que o número restrito de estudos limitou o poder estatístico das análises de subgrupos e das análises para avaliação de viés de publicação. De forma que os resultados dessas análises, em particular, precisam ser interpretados com cautela e não podem ser considerados conclusivos.

Assim, fica clara a necessidade de mais ensaios clínicos que possam fornecer mais dados e responder importantes perguntas de pesquisa. Novos estudos serão fundamentais para avaliar a eficácia e a segurança a curto e a longo prazo de diferentes tipos de estimulantes, avaliar desfechos respondidos por diferentes informantes, avaliar o impacto em desfechos funcionais (ex., desempenho acadêmico, funcionamento global), bem como para avaliar fatores moderadores e mediadores do efeito dos tratamentos.

5.3 Artigo 3

Validation of an irritability measure in preschoolers in school-based and clinical Brazilian samples.

European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-020-01701-6

ORIGINAL CONTRIBUTION

Validation of an irritability measure in preschoolers in school-based and clinical Brazilian samples

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Abstract
The Affective Reactivity Index (ARI) is an irritability measure with good psychometric properties. However, there are no published studies in preschool children, an important population in which to differentiate normative from non-normative irritability. The goal of this study was to validate the ARI in preschoolers. Two samples were included: a school-based sample ($N = 487$, mean age = 57.80 ± 7.23 months, 52.8% male) and a clinical sample of children with Attention Deficit Hyperactivity Disorder (ADHD; $N = 153$, mean age = 60.5 ± 7.6 months, 83.7% males). Confirmatory factor analysis assessed ARI unidimensionality. ARI criterion validity was tested through comparison to other scales measuring irritability, related constructs, and other aspects of psychopathology. Test–retest reliability was assessed in the school-based sample. Analyses confirmed a single-factor structure and good internal consistency. The ARI showed stronger correlations with irritability measures than with measures of other constructs. In the clinical sample, ADHD children with comorbid disruptive behavior disorders had higher ARI scores than those without this comorbidity. In the school-based sample, test–retest reliability was moderate. This is the first study to demonstrate ARI validity and reliability in preschoolers. The scale performed well in both school-based and clinical samples. Having a concise and validated irritability measure for preschoolers may facilitate both clinical assessment and research on early irritability.

Keywords Irritability · Preschool · Validity · Reliability · Psychometric properties

Introduction

Irritability can be defined as increased proneness to experiencing anger, relative to peers [1]. Clinically significant irritability often occurs in response to frustration and differentiating it from normative responses can be particularly challenging in the preschool population, where temper outbursts are common. Despite these challenges, studies demonstrate that is possible to identify clinically significant irritability in preschoolers e.g., when outbursts are frequent, qualitatively severe, or occur in unexpected contexts [2, 3]. Early identification and intervention can diminish current impairment and potentially prevent future psychopathology. Thus, it is important to have a short, standardized, and accessible scale to assess irritability among preschoolers. The Affective Reactivity Index (ARI) is a brief scale that is rated by parents and youth and designed to be used in both clinical care and research [4]. Although it has been used in multiple studies, to our knowledge, its validity in preschool children has not been assessed. Therefore, the goal of this study is to validate the ARI in two preschool samples, one school-based and the other a clinical sample of children with ADHD.

In the Diagnostic and Statistical Manual of Mental Disorders: DSM-5 [5], irritability is a diagnostic criterion for several psychiatric disorders, including Disruptive Mood Dysregulation Disorder (DMDD), Oppositional Defiant Disorder (ODD), Generalized Anxiety Disorder (GAD), Posttraumatic Stress Disorder (PTSD), Maniac/Hypomanic and Major Depressive Episodes (the latter only for children and adolescents). And, it is described as an associated feature of Attention Deficit Hyperactivity Disorder (ADHD),

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a common disorder that typically emerges during the preschool years [6, 7]. Previous studies indicate that irritability in children 3–6 years old is concurrently and longitudinally associated with functional impairment and increased risk for psychiatric disorders, including ODD, depression, and anxiety disorders [3, 8, 9]. Wakschlag et al., using the Temper Loss scale of the parent-completed multidimensional assessment profile of disruptive behavior (MAP-DB), characterized the normal–abnormal spectrum of irritability in a sample of 1490 preschool children [3]. Based on item response theory analyses, they differentiated normative misbehaviors (e.g., being easily frustrated) from qualitatively atypical behaviors (e.g., break or destroy things during a temper tantrum), and identified frequency thresholds that indicated clinical problems. While 83.7% of preschoolers in the study had tantrums "sometimes", only 8.6% presented them daily [10]. These findings provide empirical data about early irritability and its dimensional characteristics, allowing the identification of both children with severe problems and those who present more subtle symptoms but are at increased risk of developing impairment over time. Additionally, this dimensional approach can be used in studies that investigate neural processes underlying preschool irritability and thus facilitate the development of mechanism-based interventions [11, 12].

The ARI is another relevant irritability measure. It has been used in clinical trials [13], neuroimaging [14], genetic [15] and longitudinal studies [16]. However, there are no published studies in preschool children. The ARI is a narrowly focused scale that examines the child's threshold for an angry reaction and the frequency and duration of angry feelings and behaviors. It is concise and contains simple questions, so that it can be used as a screening tool in clinical settings and epidemiologic studies. It has parent and self-report versions, which have been validated in clinical and non-clinical samples in several countries and translated into 15 languages [4, 17–19]. Studies in school age children and adolescents have shown good internal consistency (self-report: Cronbach's alpha: 0.84–0.90; parent-report: Cronbach's alpha: 0.80–0.92) [4, 17, 18] and satisfactory test–retest reliability (self-report, ICC: 0.66; parent report, ICC = 0.82) [18]. Compared to the self-report, the parent-ARI has better stability and better fit in a single-factor model [4]. However, both versions have good convergent validity and can discriminate children with different psychopathologies [4, 18]. As described by DeSousa et al. [19], the translation and cross-cultural adaptation of the ARI Brazilian Portuguese version was constructed using a multi-step process and then validated in a sample of 133 children aged 8–17 years. The Brazilian Portuguese ARI maintained the original unidimensional structure and had good internal consistency (Cronbach's alpha = 0.84) and adequate validity.

The goal of this study was to validate the ARI in preschool children. As the ARI is designed to be used in both clinical and epidemiological settings, we tested it in both a school-based sample and in a clinical sample of preschool children with ADHD. First, we evaluated the construct validity of the ARI and confirmed its unidimensionality using confirmatory factor analyses (CFA). Second, we assessed criterion validity using well-validated scales as comparators. We expected that the ARI would show stronger correlations with other irritability measures than with measures designed to assess other constructs, such as anxiety, depressive symptoms, aggression and oppositionality. Third, we compared ARI scores across different levels of impairment and different clinical groups. We expected to find higher ARI scores in more impaired groups and among ADHD children with comorbid Disruptive Behavior Disorders [DBD; i.e., Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD)]. Finally, we assessed reliability using Cronbach's alpha, the Composite Reliability Index, and intra-class correlation coefficient. We expected the ARI to show good internal consistency and test–retest reliability.

Methods

Participants and procedures

School-based sample

This sample was part of the "Randomized Clinical Trial comparing executive function and language skills training on school readiness in preschool children", a pragmatic, cluster, randomized clinical trial developed at the Institute of Psychiatry of the Hospital of Clinics of the University of Sao Paulo Medical School (IPq, HC-FMUSP) and designed to evaluate two preschool curricular programs: one focused on language development and one focused on executive functions (NCT02807831). The project was approved by the HC-FMUSP Ethical Committee and parents or caregivers of all children signed informed consent. Both programs were implemented in the city of São Caetano do Sul, SP (Brazil), which has the highest Human Development Index (HDI) in the country (0.862) [20]. Twenty-seven out of 30 preschools in the city participated. One classroom per school was randomized to one of the three groups: language program (nine classes), executive function program (nine classes) or control group (nine classes). The final sample included 582 children (mean age = 57.23 ± 6.93 months, 53.6% male). Here, we present data on 487 subjects who had complete parent ARI data at baseline (mean age = 57.80 ± 7.23 months, 52.8% male). For these participants, 359 (73.7%) of the questionnaires were answered by mothers, 92 (18.9%) by fathers,

32 (6.6%) by another caregiver, and for 4 participants the information was missing. In addition to the ARI, parents completed the Swanson, Nolan, and Pelham-IV (SNAP-IV) [21] and the child behavior check List 1.5–5 (CBCL) [22]. Children's psychological function was assessed at baseline and at the end of the trial, after 15 weeks [23]. For the control group ($N = 156$), the baseline and final-ARI were used to assess test–retest reliability.

Clinical sample

This sample was part of the "Medication and parent training study for preschoolers with ADHD" (Mappa Study), a double-blind, randomized placebo-controlled trial designed to compare methylphenidate parent training and placebo plus educational intervention in the treatment of preschool children with ADHD (NCT02807870). The study was developed at IPq, HC-FMUSP and approved by the HC-FMUSP Ethical Committee. Participants were recruited through a website and through letters and advertisements sent to schools and published in social media. Parents or caregivers of all participants signed the informed consent. The inclusion criteria were age 47–71 months, ADHD diagnosis, IQ ≥ 70, CGAS < 70, and enrolled in school or day-care. DSM-5 ADHD diagnosis was established by a child and adolescent psychiatrist using the Kiddie Schedule for Affective Disorders-present and lifetime version (KSADS-PL) [24, 25]. Children using psychotropic medications were excluded. The sample consisted of 153 preschool children (mean age = 60.5 ± 7.6 months, 83.7% males) who were randomized into 3 groups: methylphenidate plus educational intervention ($n = 51$), parent training plus placebo medication ($n = 51$), and placebo medication plus educational intervention ($n = 51$). At baseline, 144 (94.1%) of the questionnaires were answered by mothers, 7 (4.6%) by fathers, and 2 (1.3%) by another caregiver. In addition to the ARI, parents completed: the SNAP-IV [21]; the MAP-DB [26], and the Children's Behavior Questionnaire (CBQ) [27].

Measures

Affective reactivity index (ARI)

The ARI is a parent and a self-reported measure of irritability for children and adolescents. It includes six items assessing feelings and behaviors related to irritability and one item assessing impairment due to irritability (i.e., "Overall, irritability causes him/her problems"). For the first six items, responses are on a three-point Likert scale: 'not true', 'somewhat true', 'certainly true', scored as '0', '1', '2', respectively. The total score is the sum of the six items, ranging from 0 to 12. Level of impairment is classified into three categories, according to the responses: 'not true', 'somewhat true', 'certainly true'. In this study, the Brazilian Portuguese version of the parent ARI was used [19].

Swanson, Nolan, and Pelham-IV (SNAP-IV)

The SNAP-IV was used in both school-based and clinical samples. It is a 26-item scale used to assess ADHD and ODD symptoms. It has been translated into Brazilian Portuguese and it has been validated in a Brazilian sample [28, 29]. In this study, we included the SNAP inattention and hyperactivity/impulsivity dimensions (School-based sample, Cronbach's alpha = 0.76 and 0.79; Clinical sample, Cronbach's alpha = 0.82 and 0.85). And, consistent with previous study [30], we used three SNAP ODD items (i.e., "Loses temper"; "Is touchy or easily annoyed by others"; and "Is angry and resentful") to generate the SNAP irritability measure, with scores ranging from 0 to 9 (school-based sample, Cronbach's alpha = 0.54; clinical sample, Cronbach's alpha = 0.74). Other four SNAP ODD items (i.e.: "Argues with adults", "Actively defies or refuses adult requests or rules", "Does things deliberately that annoy other people", and "Blames others for his or her mistakes or misbehavior") were used to generate the SNAP headstrong measure, with scores ranging from 0 to 12 (school-based sample, Cronbach's alpha = 0.68; clinical sample, Cronbach's alpha = 0.77). In previous study, both measures presented good internal consistency (SNAP irritability, Cronbach's alpha = 0.83; SNAP headstrong, Cronbach's alpha = 0.83), and good convergent validity [30].

Child behavior checklist 1.5–5 (CBCL)

The CBCL 1.5–5 was used only in the school-based sample. It is a 99-item scale used to assess children's psychopathology. It has been translated into Brazilian Portuguese and it has shown good internal consistency (Cronbach's alpha range: 0.69–0.94) and test–retest reliability [31, 32]. For this study, we used the CBCL Anxious/Depressed (Cronbach's alpha: 0.59), the CBCL Attention Problems (Cronbach's alpha: 0.60) scales; and, consistent with previous studies [18, 33, 34], we used three CBCL items (i.e., "temper tantrums or hot temper", "stubborn, sullen or irritable", and "sudden changes in mood or feelings") to compute the CBCL irritability variable, with scores ranging from 0 to 6 (Cronbach's alpha: 0.59). In previous studies, Cronbach's alpha between 0.61 and 0.70 have been reported for the CBCL irritability construct [33, 34].

Multidimensional assessment profile of disruptive behavior (MAP-DB)

The MAP-DB was used only in the clinical sample. The MAP-DB is a multidimensional questionnaire that assesses four dimensions of disruptive behaviors (i.e., temper loss, aggression, noncompliance and low concern to others) [26]. Here, the MAPDB temper loss dimension was used as a measure of irritability and the other dimensions as comparators [11, 12]. The translation and cross-cultural adaptation to Brazilian Portuguese of the MAP-DB used a multi-step process similar to that in DeSousa et al. [19]. But, it has not been validated or used previously in Brazilian samples. In our clinical sample, we found Cronbach's alpha between 0.89 and 0.96. Similar to what have been reported in previous study (Cronbach's alpha = 0.92–0.97) [26].

Children's Behavior Checklist (CBQ).

The CBQ short-form was used only in the clinical sample. It has 94 items that assess 15 temperament domains. The Brazilian Portuguese version has been used previously in Brazilian samples [35, 36], but has not been validated. In this study, we used the CBQ anger/frustration (Cronbach's alpha: 0.78) and CBQ activity level (Cronbach's alpha: 0.56) scales.

Data analysis

The analyses for each sample were conducted separately but followed the same procedure.

CFA was used to confirm the unidimensional structure of the ARI. Considering the categorical nature of the items, we used the weighted least square mean variance (WLSMV) estimation method. Analyses were conducted using the Lavaan package in R [37]. To assess model fit, the following indices were used: comparative fit index (CFI), Tucker–Lewis index (TLI), and root mean square error of approximation with 90% confidence interval (RMSEA-90% CI). CFI and TLI values above 0.95 and RMSEA values close to or below 0.06 indicated good fit [38], and RMSEA values below 0.08 indicated acceptable fit [39].

Pearson correlation was used to assess associations between the ARI and other measures, specifically SNAP irritability, headstrong, inattention, hyperactivity/impulsivity; CBCL irritability, anxious/depressed, and attention problems; MAP-DB temper loss, aggression, noncompliance and low concern to others; and CBQ anger/frustration and activity level. Differences between correlation coefficients were tested using Fisher's *r*-to-*z* transformations [40]. We expected that ARI scores would have stronger correlations with irritability measures (i.e., SNAP irritability, CBCL irritability, MAP-DB temper loss scale) than with a measure of oppositionality (i.e., SNAP headstrong), and irritability-related constructs (i.e., CBCL anxious/depressed, MAP-DB aggression). In both samples, one-way analyses of variance (ANOVAs) were used to investigate differences in parent ARI scores among the three categories of ARI impairment. In the clinical sample, a one-way ANOVA was also used to assess differences in ARI scores among ADHD children without comorbidities; ADHD children with ODD/CD comorbidity; and ADHD children with comorbidities other than ODD/CD.

To assess reliability, in both samples, the Cronbach's alpha and the Composite Reliability Index (CRI) were used to measure internal consistency. In contrast to Cronbach's alpha, the CRI does not assume that all items add equally to the reliability of the factor. Instead, it takes into account the standardized loadings and the measurement errors of each item. CRI values > 0.70 are considered satisfactory [41]. In the school-based sample, we used pre-and post-intervention data from the control group to assess test–retest reliability. The interval between the two assessments was 15 weeks. To calculate the intraclass correlation coefficient ($ICC_{A,1}$), we used a two-way mixed-effect analysis of variance model with interaction for the absolute agreement between single scores [42, 43]. Because the three groups in the clinical sample received an intervention, test–retest reliability was not assessed.

Results

Descriptive statistics

Table 1 presents demographic and clinical characteristics of the school-based and clinical ADHD samples; for the latter, ADHD sub-type and psychiatric comorbidities are also described. Table 2 provides means and standard deviations of the irritability measures. As expected, the clinical sample had higher ARI [$F(1,222.19) = 156.53$; $p < 0.0005$] and SNAP irritability scores [$F(1,218.37) = 76.12$; $p < 0.0005$] than the school-based sample. Also, 80.4% of parents in the clinical sample, compared to 19.5% of parents in the school-based sample, answered positively to the item "Overall, irritability causes him/her problems". Again, as expected, all ARI items were more frequently endorsed in the clinical than the school-based sample. In both samples, the items "Often loses his/her temper" and "loses temper easily" were most commonly endorsed, while "stays angry for a long time" and "is angry most of the time" were the least common (Table 2).

Table 1 Demographics and clinical characteristics of the school-based and the clinical sample

	School-based sample ($N=487$)	Clinical sample ($N=153$)
Age (m), mean (SD), [Range]	57.80 (7.23), [43–79]	60.45 (7.60), [47–71]
Gender male, *N* (%)	257 (52.8)	128 (83.7)
IQ child (WPPSI-IIV), mean (SD)	–	90.14 (11.16)
Mother's school attainment, *N* (%)		
Middle school incomplete	32 (6.6)	12 (7.8)
Middle school complete	46 (9.5)	17 (11.1)
High school complete or technical	257 (53.1)	67 (43.8)
Graduation complete	149 (30.8)	57 (37.3)
Monthly income (R$), *N* (%)		
≤1200	42 (8.8)	27 (25.7)
1201–2400	104 (21.7)	32 (30.5)
2401–4800	182 (37.9)	32 (30.5)
4801–6000	68 (14.2)	7 (6.7)
6001–10,000	60 (12.5)	6 (5.7)
≥10,001	24 (5.0)	1 (1.0)
SNAP parents, mean (SD)		
ADHD TOTAL	15.76 (7.80)	35.89 (8.89)
ODD total	5.30 (3.57)	9.61 (4.96)
ADHD sub-type, *N* (%)		
Inattention	–	11 (7.2)
Hyperactivity/impulsivity	–	34 (22.2)
Combined	–	108 (70.6)
Number of comorbidities, *N* (%)		
0	–	57 (37.3)
1	–	55 (35.9)
2	–	25 (16.3)
≥3	–	16 (10.5)
Comorbidities, *N* (%)		
ODD	–	65 (42.5)
Conduct disorder	–	15 (9.8)
Simple phobia	–	31 (20.3)
Other anxiety disorders (SAD/social phobia /GAD)	–	15 (9.8)
Enuresis/encopresis	–	19 (12.4)
Other disorders (Tics, OCD, MDD)	–	11 (7.2)

ADHD Total = Inattention + Hyperactivity/Impulsivity symptoms

GAD Generalized Anxiety Disorder, *MDD* Major Depressive Disorder, *OCD* Obsessive Compulsive Disorder, *ODD* Oppositional Defiant Disorder, *SAD* Separation Anxiety Disorder; *SNAP* Swanson, Nolan, and Pelham-IV, *WPPSI-IIV* The Wechsler Preschool and Primary Scale of Intelligence

Construct validity

CFA demonstrated that a one-factor solution was an adequate description of the data in both samples [school-based sample: CFI = 0.99, TLI = 0.98 RMSEA = 0.07 (90% CI 0.05–0.10); clinical sample: CFI = 1.0, TLI = 0.99, RMSEA = 0.06 (90% CI 0.00–0.12)]. In the school-based sample, all items had factor loadings greater than 0.52; in the clinical sample, all items had factor loadings greater than 0.65 (Table 2).

Criterion validity

Pearson correlations showed that, in both samples, ARI score correlated moderately with other irritability measures (i.e., SNAP irritability, CBCL irritability, MAP-DB temper loss scale, *r* range 0.55–0.68). There were also moderate correlations between the ARI and irritability related constructs (i.e., CBCL anxious/depressed, MAP-DB aggression, CBQ anger/frustration; *r* range 0.43–0.59) and measures of oppositionality (i.e., SNAP headstrong and MAP-DB noncompliance; *r* range 0.40–0.49) (Table 3). In contrast, the ARI had

Table 2 Mean item and total scores, frequency of response and factor loadings for the affective reactivity index; and mean scores for other irritability measures

	Mean (SD), [Range]	Frequency of response (%)			Factor loadings
		Not true	Somewhat true	Certainly true	
School-based sample ($N=487$)					
ARI					
1. Is easily annoyed by others	0.53 (0.70)	58.9	29.2	11.9	0.55
2. Often loses his/her temper	0.69 (0.74)	47.2	36.3	16.4	0.85
3. Stays angry for a long time	0.33 (0.58)	72.9	21.4	5.7	0.52
4. Is angry most of the time	0.11 (0.39)	91.2	6.4	2.5	0.73
5. Gets angry frequently	0.49 (0.66)	60.4	30.2	9.4	0.87
6. Loses temper easily	0.55 (0.69)	56.4	32.5	11.1	0.85
ARI total	2.70 (2.65), [0–12]				
ARI impairment: "Overall, irritability causes him/her problems"	0.25 (0.55)	80.5	13.8	5.7	
SNAP irritability	2.39 (1.78), [0–9]				
CBCL irritability	2.01 (1.41), [0–6]				
Clinical sample ($N=153$)					
ARI					
1. Is easily annoyed by others	0.92 (0.70)	28.8	50.3	20.9	0.65
2. Often loses his/her temper	1.45 (0.66)	9.2	36.6	54.2	0.93
3. Stays angry for a long time	0.80 (0.73)	38.6	43.1	18.3	0.80
4. Is angry most of the time	0.43 (0.58)	61.4	34.0	4.6	0.85
5. Gets angry frequently	1.07 (0.58)	23.5	46.4	30.1	0.83
6. Loses temper easily	1.26 (0.72)	16.3	41.2	42.5	0.85
ARI total	5.93 (3.18), [0–12]				
ARI impairment: "Overall, irritability causes him/her problems"	1.26 (0.77)	19.6	34.6	45.8	
SNAP irritability	3.92 (2.21), [0–9]				
MAP-DB temper loss	34.90 (20.86), [0–104]				

CBCL child behavior check list 1.5–5, *SNAP* Swanson, Nolan, and Pelham-IV, *MAP-DB* multidimensional assessment profile of disruptive behavior

Table 3 Pearson correlation between Affective Reactivity Index Score and other irritability-related measures

	ARI total score (r)
School-based sample	
SNAP irritability	0.58[a]
SNAP headstrong	0.49[a]
CBCL irritability	0.55[a]
CBCL anxious/depressed	0.43[a]
Clinical sample	
SNAP irritability	0.68[a]
SNAP headstrong	0.46[a]
MAP-DB temper loss	0.62[a]
MAP-DB aggression	0.47[a]
CBQ anger/frustration	0.59[a]

CBCL child behavior check list 1.5–5, *CBQ* Children's Behavior Questionnaire, *SNAP* Swanson, Nolan, and Pelham-IV, *MAP-DB* multidimensional assessment profile of disruptive behavior

[a]Correlation is significant at the 0.01 level (two-tailed)

low correlations with SNAP, CBCL, MAP-DB and CBQ constructs that were not related specifically to irritability (i.e., SNAP inattention and hyperactivity/impulsivity, CBCL attention problems, MAP-DB low concern to others, CBQ activity level; r range 0.19–0.39) [44].

As expected, in both samples, Fisher's r-to-z transformations indicated that the ARI correlation with SNAP irritability was stronger than the ARI correlation with SNAP headstrong (school-based sample: z score = 2.50, $p = 0.01$; clinical sample: z score = 4.06, $p < 0.001$). In the school-based sample, the ARI correlation with CBCL irritability was stronger than the ARI correlation with the CBCL anxious/depressed subscale (z score = 3.09, $p = 0.002$). And, in the clinical sample, the ARI correlation with MAP-DB temper loss was stronger than the ARI correlation with MAP-DB aggression (z score = 3.20, $p = 0.001$).

In both samples, one-way ANOVAs indicated that ARI scores differed across the three categories of ARI impairment [school-based sample: $F(2,55.94) = 78.77$;

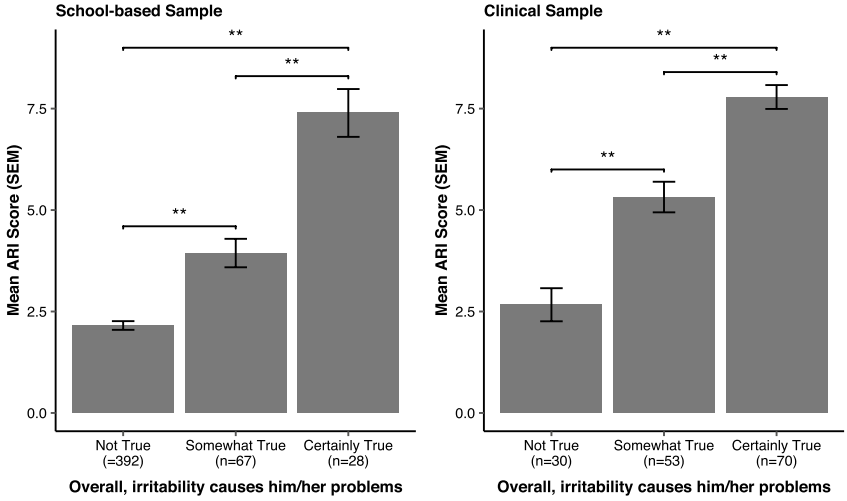

Fig. 1 Affective Reactivity Index mean scores by impairment category. $^{**}p < 0.005$. *SEM* standard error of the mean

p value < 0.0005; clinical sample: $F(2,150) = 45.61$; $p < 0.0005$], with increased impairment associated with increased irritability (Fig. 1). In the clinical sample, a one-way ANOVA indicated that ARI scores differed among ADHD children with comorbid ODD or CD, ADHD children with comorbidities other than ODD/CD, and ADHD children without comorbidity [$F(2,150) = 14.73$; $p < 0.0005$]. Post hoc pairwise comparisons indicated that the ODD/CD group had higher irritability scores than children with comorbidities other than ODD/CD (2.03, 95% CI 0.45–3.61, $p = 0.007$), and than children without comorbidities (2.81, 95% CI 1.49–4.12, $p < 0.0005$) (Fig. 2).

Reliability

In both samples, the ARI had good internal consistency. In the school-based sample, Cronbach's alpha was 0.78 and the Composite Reliability Index was 0.88. In the clinical sample, Cronbach's alpha was 0.86 and the Composite Reliability Index was 0.94. In the school-based sample, test–retest $ICC_{A,1}$ for the total ARI score was 0.55 (95% CI 0.42–0.66).

Discussion

To our knowledge, this is the first study to examine validity of the ARI in preschool children; importantly, we tested validity in both a school-based sample and a clinical sample. As expected, in both samples, we confirmed ARI unidimensionality and demonstrated good validity and reliability. The results extend previous findings on the psychometric properties of the ARI in older youth and suggest that it can be used

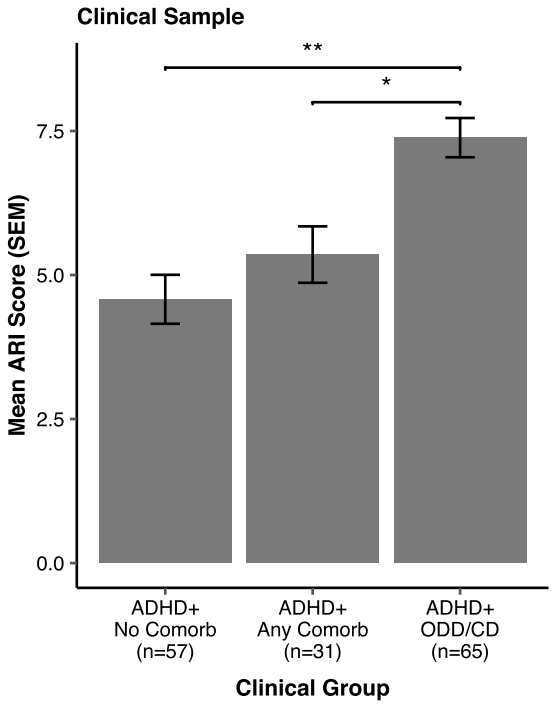

Fig. 2 Affective Reactivity Index mean scores by clinical group. $^{*}p = 0.007$; $^{**}p < 0.005$. ADHD + No Comorb = Children with ADHD and no comorbidity; ADHD + Any Comorb = Children with ADHD and any comorbidity, except Oppositional Defiant Disorder or Conduct Disorder; ADHD + ODD/CD = Children with ADHD and Oppositional Defiant Disorder or Conduct disorder and any other comorbidity, if present; SEM = standard error of the mean

to assess irritability in both clinical and non-clinical samples of preschool children.

Consistent with previous studies showing an association between high levels of irritability and psychiatric problems in preschoolers [8, 10], we found higher levels of both irritability and impairment in the clinical vs. the school-based sample. Moreover, in both samples, items "often loses temper" and "loses temper easily" were the most frequently endorsed by parents and the items "stays angry for a long time" and "is angry most of the time" were the least endorsed. These results were expected, as temper outbursts occur normatively during preschool [2]. They were also consistent with Copeland et al. [45], who assessed a sample of 1420 children aged 9–16 years and showed that phasic irritability (i.e., temper outbursts) was more frequent than tonic irritability (i.e., chronically angry mood between outbursts), and that tonic irritability rarely presented without phasic irritability. It is interesting to note that only 9% of the parents in the school-based sample answered positively to the item "is angry most of the time", compared to 38.6% in the clinical sample, suggesting that this behavior is uncommon during preschool and may be a marker of psychopathology.

Consistent with data in older samples, the one-factor model fit well in both samples here and all items showed good factor loadings. With respect to criterion validity, ARI scores were moderately correlated with irritability measures, as well as with related constructs and measures of oppositionality. In contrast, ARI scores had low correlations with constructs that were not related specifically to irritability. As expected, the ARI correlation with other irritability measures, i.e., SNAP irritability, CBCL irritability, and MAP-DB temper loss, was stronger than the ARI correlation with SNAP headstrong, CBCL anxious/depressed subscale, and MAP-DB aggression, respectively. Altogether, these findings provide evidence of ARI criterion validity and are consistent with previous studies that analyzed multidimensional models of disruptive behaviors and characterized irritability, aggression and oppositionality as distinct dimensions [46–48].

In the clinical sample, the ARI was able to discriminate ADHD children with ODD/CD comorbidity from ADHD children without comorbidity or with comorbidities other than ODD/CD. All three groups had irritability symptoms reported by parents. Previous studies have shown high rates of irritability in children with ADHD [49, 50], and irritable/angry mood is one dimension of the ODD diagnostic criteria [5]. Thus, while the ARI is obviously not a diagnostic tool, these findings underscore its dimensional characteristics and clinical utility for the assessment of preschool children with different psychopathologies.

In both samples, ARI had good internal consistency. And, in the school-based sample, test–retest reliability was moderate [51]. However, the ARI test–retest coefficient (ICC = 0.55) was lower than that previously reported in a clinical sample of older youth (ICC = 0.82) [18] and in a sample of adults (ICC = 0.80) [17]. This result may indicate that the ARI is less stable in preschoolers, or it may reflect a longer interval between assessments, i.e., 15 weeks as compared to 1–2 weeks in previous studies [52]. It is also possible that, because of developmental factors, irritability symptoms during preschool are less stable than those later in life [53]. Regarding other measures used to assess irritability in preschoolers, Wakschlag et al. [3], using the MAP-DB, reported a longitudinal correlation of 0.71 over 9 months in a sample of 497 children (mean age = 4.2 years). Dougherty et al. [8] used six items from the Preschool Age Psychiatric Assessment (PAPA), corresponding to the six items from the ARI, to assess irritability in 462 children aged 3–6 years old and found moderate stability ($r_s = 0.38$). We could not assess test–retest reliability in our clinical sample, because it was derived from a treatment study.

The present study has several limitations. First, because of the lack of diagnostic evaluation in the school-based sample, we could not assess the ARI's ability to discriminate children with and without psychiatric disorders in a non-clinical sample. Second, although comorbidities were allowed, all participants in the clinical sample had ADHD as their primary diagnosis. Thus, further studies should be conducted to investigate the ARI's psychometric properties in other clinical populations. Third, for some of the measures, Cronbach's alphas were in the low range of acceptance. This could have been influenced by a low number of items and ordinal format of the responses [54, 55]. Thus, the results of correlations involving these variables should be interpreted with caution. Fourth, because of the study design, test–retest reliability was assessed only in the school-based sample, and the interval between measures was long (i.e. 15 weeks). Therefore, more studies are needed to confirm ARI stability during preschool. Fifth, because our data are cross-sectional, we could not assess predictive validity. Sixth, in both samples, all measures were reported by parents or caregivers and no information was obtained from teachers, potentially adding biases to the results. In addition, given the age of the participants, we did not use the ARI self-report. Although the ARI was originally developed as a parent- and self-report measure, a recent study reported good psychometric properties for the ARI completed by teachers of children 7–11 years old [56]. And, a clinician-rated version of the ARI was developed and validated in school aged children and adolescents [57]. Future studies validating teachers' responses and the Clinician ARI in preschoolers would allow comparisons among informants and facilitate the assessment of early irritability in different contexts.

In conclusion, this is the first study to demonstrate validity and reliability of the ARI in preschoolers, expanding ARI use from early childhood to adulthood. Importantly, data

were included from both a school-based sample and a clinical sample. Except for the test–retest reliability, ARI psychometric properties found in our preschool samples were similar to what was previously reported in studies with school age children and adolescents. Although the findings require replication, this brief and reliable assessment tool should facilitate investigations about early irritability in clinical and non-clinical samples of preschoolers. Future longitudinal studies using the ARI across the lifespan may contribute to our understanding of the developmental characteristics of irritability.

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Compliance with ethical standards

Conflict of interest Dr. Polanczyk, in the last 3 years, has been a consultant, member of advisory board, and/or speaker for Shire/Takeda, Medice, Aché, Novo Nordisk and Pfizer; and he has received travel expenses for continuing education support from Shire/Takeda and royalties from Editora Manole. Dr. Stringaris has developed the ARI with his colleagues and has made it openly available for free use. The other authors have no conflicts of interest to disclose.

Ethical standards The "Randomized Clinical Trial Comparing Executive Function and Language Skills Training on School Readiness in Preschool Children" (NCT02807831), and the "Medication and Parent Training Study for Preschoolers with ADHD" (Mappa Study, NCT02807870) were approved by the HC-FMUSP Ethical Committee. In accordance with the declaration of Helsinki, parents or legal representatives of all children were informed about the research and provided written consent.

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5.3.1 Discussão artigo 3

O estudo intitulado *"Validation of an irritability measure in preschoolers in school-based and clinical Brazilian samples"* teve como objetivo validar o uso da versão em português da escala *Affective Reactivity Index (ARI)* em duas amostras de crianças pré-escolares brasileiras.

A ARI é uma escala que se destaca por ser um instrumento bastante utilizado para avaliação de irritabilidade, por já ter sido traduzido em mais de 15 línguas e por já ter sido validada em diferentes países, incluindo Estados Unidos, Espanha, China, Austrália e Brasil. No entanto, este foi o primeiro estudo a demonstrar a validade e confiabilidade da ARI em amostras de crianças pré-escolares, incluindo uma amostra da comunidade e uma amostra clínica de crianças com TDAH. Mais recentemente, Wilson et al. (2022) [87] também publicaram um estudo que avaliou o uso da ARI em crianças de 3-8 anos, corroborando a utilidade deste instrumento para avaliação de irritabilidade em crianças mais jovens.

Ter um instrumento conciso, com boas propriedades psicométricas e validado para uso em crianças pré-escolares é fundamental para a realização de estudos sobre irritabilidade precoce. Além disso, o fato de a ARI ser adequada para avaliação de irritabilidade em diferentes faixas etárias também permite que ela seja utilizada em estudos longitudinais que investiguem a sua trajetória.

A validação da versão em português da ARI em amostras brasileiras também é importante, pois abre o caminho para o desenvolvimento de pesquisas sobre irritabilidade precoce no Brasil. Assim como pode, futuramente, facilitar a colaboração com pesquisadores internacionais e permitir o desenvolvimento de pesquisas transculturais. Esta é uma área ainda pouco explorada, que tem despertado interesse entre os pesquisadores. Como exemplo disso, recentemente, foi criado o *Cross-Cultural Consortium on Irritability,* iniciativa liderada pela Dra. Wang Lin Tseng e pela Dra. Ellen Leibenluft, com objetivo de reunir pesquisadores de diferentes países e promover o desenvolvimento deste campo, da qual a candidata faz parte.

6 DISCUSSÃO FINAL

Esta tese teve como objetivo avançar o conhecimento sobre o TDAH na idade pré-escolar, particularmente sobre os efeitos das diferentes modalidades de tratamento e sobre a avaliação de irritabilidade. Para tanto, foi realizado o 'Estudo Mappa', um ensaio clínico randomizado, duplo-cego, controlado por placebo e controlado por treinamento parental-*sham* que avaliou a eficácia e segurança do uso de metilfenidato e treinamento parental para tratamento de crianças pré-escolares com TDAH (artigo 1). Como forma de aprofundar o estudo sobre tratamento de crianças pré-escolares com TDAH e levando em consideração publicações feitas durante o período em que se desenvolveu o doutorado, foi realizada uma revisão sistemática e meta-análise que teve como objetivo sintetizar as evidências disponíveis na literatura sobre o uso de estimulantes para tratamento de crianças pré-escolares com TDAH (artigo 2). Em conjunto, estes dois estudos demonstram que o uso estimulantes é eficaz na redução dos sintomas de TDAH e fornecem evidências que podem informar as recomendações de tratamento para crianças pré-escolares com TDAH.

No entanto, o número limitado de ensaios clínicos identificados pela revisão sistemática e incluídos na meta-análise deixa evidente a necessidade de haver mais ensaios clínicos sobre o uso de estimulantes para tratamento de crianças pré-escolares com TDAH. No futuro, novos ensaios clínicos serão fundamentais para avaliar a eficácia, aceitabilidade e tolerabilidade do uso de diferentes estimulantes a curto e a longo prazo, avaliar o efeito de tratamentos em desfechos funcionais, avaliar o efeito de fatores mediadores e moderadores e avaliar a eficácia do tratamento combinado de estimulantes e treinamento parental.

Por fim, a validação da escala ARI, realizada em função da falta de instrumentos para avaliação de irritabilidade em crianças pré-escolares (artigo 3), não só amplia o uso desta escala para crianças pré-escolares como pode, no futuro, contribuir para o desenvolvimento de pesquisas sobre irritabilidade precoce no Brasil, uma área relevante de pesquisa, ainda pouco desenvolvida no país.

7 CONCLUSÕES

O conjunto de estudos apresentados nesta tese aponta para a segurança e eficácia dos estimulantes na redução dos sintomas de TDAH e para efeitos específicos em desfechos secundários. Primeiro, o 'Estudo Mappa' mostra que metilfenidato é eficaz na redução dos sintomas de TDAH e na melhora da funcionalidade global, e que treinamento parental comportamental é eficaz na melhora da funcionalidade global de crianças em idade pré-escolar com TDAH, em 8 semanas de tratamento. Análises de desfechos secundários também mostraram que metilfenidato melhora a performance em testes cognitivos de atenção, enquanto TPC reduz irritabilidade. Os resultados da meta-análise corroboram os achados do 'Estudo Mappa' e mostram que os estimulantes são eficazes na redução dos sintomas de TDAH entre crianças em idade pré-escolar. Em conjunto, esses resultados suportam o uso de estimulantes no tratamento para pré-escolares com TDAH e questionam diretrizes que recomendam treinamento parental comportamental como primeira linha de tratamento para crianças pré-escolares com TDAH.

Além disso, o estudo sobre a validação da escala ARI mostrou que a versão em português desta escala apresenta adequada validade e confiabilidade na avaliação de crianças pré-escolares, indicando que este pode ser um instrumento bastante útil para o estudo sobre irritabilidade precoce no Brasil.

Assim, esta tese contribui para a tomada de decisão clínica e para a formulação de diretrizes de tratamento para crianças pré-escolares com TDAH. E contribui para o avanço do conhecimento e a realização de novas pesquisas sobre TDAH e irritabilidade na idade pré-escolar.

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9 APÊNDICE

9.1 Apêndice 1: tradução e retrotradução da escala *Multidimensional Assessment Profile – Disruptive Behavior (MAP-DB)*

O processo de tradução e adaptação da escala *Multidimensional assessment profile of disruptive behavior* (MAP-DB) para o português do Brasil foi realizado em duas etapas. Primeiro, foi realizada a tradução e retrotradução da escala. Neste processo, a escala MAP-DB foi traduzida do inglês para o português do Brasil por dois tradutores independentes, e ambas as traduções foram sintetizadas em uma única versão em português do Brasil por um terceiro tradutor independente. Na sequência, essa versão sintetizada foi retrotraduzida por dois outros tradutores independentes, e um terceiro tradutor sintetizou ambas as retrotraduções em uma única versão em inglês. Todos os tradutores envolvidos nesse processo eram fluentes nos dois idiomas.

Na segunda etapa, as traduções e retrotraduções foram revisadas por especialistas, incluindo a Dra. Lauren Wakschlag, uma das autoras da escala MAP-DB. Nesse momento, foi avaliado se a tradução estava adequada e se os itens traduzidos eram semanticamente equivalentes a escala original. Ajustes da versão em português do Brasil foram realizados após consenso entre pesquisadores.

Original MAP-DB	Translation 1 (BP)	Translation 2 (BP)	Final Translation (BP)	Back-translation 1 (E)	Back-translation 2 (E)	Final Back-translation (E)	Final Brazilian Portuguese version after discussion
In the past month, how often did your child…	No último mês, com que frequência seu filho…	No último mês, com que frequência seu filho (a)…	No último mês, com que frequência seu filho (a)…	During the last month, how often did your child…	In the last month, how often did your son/daughter….	In the last month, how often did your son/daughter….	No último mês, com que frequência seu filho (a)…
Never	Nunca	Nunca	Nunca	Never	Never	Never	Nunca
Rarely (less than once per week)	Raramente (menos de uma vez por semana)	Raramente (menos de uma vez por semana)	Raramente (menos de uma vez por semana)	Rarely (less than once a week)	Rarely (less than once a week)	Rarely (less than once a week)	Raramente (menos de uma vez por semana)
Some (1-3 days of the week)	Algumas (1-3 dias da semana)	Alguns dias (1-3 dias na semana)	Alguns dias (1-3 dias na semana)	Some days (1-3 days a week)	few days a week (1-3 d/week)	Some days (1-3 days a week)	Alguns dias (1-3 dias na semana)
Most (4-6 days of the week)	A maior parte (4-6 dias da semana)	Maior parte dos dias (4-6 dias na semana)	A maior parte dos dias (4-6 dias na semana)	Most days (4-6 days a week)	Most of the days (4-6 days/week)	Most days (4-6 days a week)	A maior parte dos dias (4-6 dias na semana)
Every day of the week	Todos os dias da semana	Todos os dias da semana	Todos os dias da semana	Every day of the week	Everyday	Every day	Todos os dias da semana
Many times each day	Várias vezes por dia	Várias vezes por dia	Várias vezes por dia	Many times in a day	Multiple times a day	Many times a day	Várias vezes por dia
Low Concern	**Pouca preocupação com outros**	**Pouca preocupação**	**Pouca preocupação**	**Low concern**	**Little worry**	**Low concern**	**Pouca preocupação com os outros**
1. Keep on doing something that was scaring or upsetting someone	1. Continuou fazendo algo que estava assustando ou chateando alguém	1. Continuou fazendo algo que estava assustando ou chateando alguém	1. Continuou fazendo algo que estava assustando ou chateando alguém	1. Kept doing something that was frightening or upsetting someone	1. Kept doing something that was scaring or upsetting someone	1. Kept doing something that was concerning or upsetting to someone	1. Continuou fazendo algo que estava assustando ou chateando alguém
2. Act like s/he did not care when someone else felt bad or sad	2. Agiu com se ela/ele não se importasse quando alguém estava se sentindo mal ou triste	2. Agiu como se ele/ela não se importasse quando outra pessoa se sentia mal ou triste	2. Agiu como se ele/ela não se importasse quando outra pessoa se sentia mal ou triste	2. Acted as if he/she didn't care when someone else felt bad or sad	2. acted as if he/she did not mind when other person felt bad or sad	2. Acted as if he/she did not care when someone felt bad or sad	2. Agiu como se ele/ela não se importasse quando outra pessoa se sentia mal ou triste
3. Enjoy making others mad	3. Divertiu-se em deixar outras pessoas furiosas	3. Gostou de deixar os outros bravos	3. Gostou de deixar os outros bravos	3. Enjoyed vexing other people	3. liked to make others angry	3. Enjoyed making others angry	3. Gostou de deixar os outros bravos
4. Not seem to care about other adults' feelings (e.g., babysitter, family member)	4. Pareceu não se importar com os sentimentos de outros adultos (por ex.: babá, familiares)	4. Não pareceu se importar com os sentimentos de outros adultos (ex. babá, membros da família)	4. pareceu não se importar com os sentimentos de outros adultos (por ex.: babá, membros da família)	4. Didn't seem to care about other people's feelings	4. seemed to not care about other people feelings (e.g.: nanny, family members)	4. Not seem to care about other adults' feelings (e.g.: babysitter, family members)	4. pareceu não se importar com os sentimentos de outros adultos (por ex.: babá, membros da família)
5. Not seem to care about your or other parent's feelings	5. Pareceu não se importar com os seus sentimentos ou com os	5. Não pareceu se importar com os seus sentimentos	5. Pareceu não se importar com os seus sentimentos ou com os	5. Didn't seem to care about your feelings or about his/her	5. seemed to not care about his/her feelings or	5. Not seem to care about his/her feelings or about	5. Pareceu não se importar com os sentimentos

	do pai/ da mãe	ou do outro progenitor	sentimentos do pai/ da mãe	father/mother's feelings	parents feelings	parent's feelings	da mãe ou do pai
6. Act like s/he did not care when someone was mad or upset	6. Agiu como se ela/ele não se importasse quando alguém estava bravo ou chateado	6. Agiu como se ele/ela não se importasse quando alguém estava bravo ou chateado	6. Agiu como se ele/ela não se importasse quando alguém estava bravo ou chateado	6. Acted as if he/she didn't care when someone was angry or upset	6. acted as if he/she did not mind when someone was angry or upset	6. Acted as if he/she did not care when someone was upset	6. Agiu como se ele/ela não se importasse quando alguém estava bravo ou chateado
7. Do things to humiliate or embarrass others	7. Fez coisas para humilhar ou envergonhar outras pessoas	7. Fez coisas para humilhar ou envergonhar outros	7. Fez coisas para humilhar ou envergonhar outros	7. Did things to humiliate or embarrass others	7. made things to humiliate or embarrass others	7. Did things to humiliate or embarrass others	7. Fez coisas para humilhar ou envergonhar outros
8. Act like s/he did not care about pleasing other people	8. Agiu como se ela/ele não se importasse em agradar outras pessoas	8. Agiu como se ele/ela não se importasse em agradar outras pessoas	8. Agiu como se ele/ela não se importasse em agradar outras pessoas	8. Acted as if he/she didn't care about pleasing other people	8. acted as if he/she did not care about pleasing others	8. Act as if he/she did not care about pleasing others	8. Agiu como se ele/ela não se importasse em agradar outras pessoas
9. Not care about other's feelings when frustrated, angry, or upset	9. Não se importou com os sentimentos dos outros, quando estava frustrado, bravo ou chateado	9. Não se importou com os sentimentos dos outros quando frustrado, bravo ou chateado	9. Não se importou com os sentimentos dos outros, quando estava frustrado, bravo ou chateado	9. Didn't care about other people's feelings when frustrated, angry or upset.	10. did not care about others feelings, when frustrated, angry or upset	9. Did not care about other's feeling when frustrated, angry or upset.	9. Não se importou com os sentimentos dos outros, quando estava frustrado, bravo ou chateado
Temper Loss	**Descontrole emocional**	**Descontrole emocional**	**Descontrole emocional**	**Emotional decontrol**	**Emotional dyscontrol**	**Lack of emotional control**	**Descontrole emocional**
1. Have difficulty calming down when angry	1. Teve dificuldade para se acalmar quando ficou bravo	1. Teve dificuldade de se acalmar quando ficou bravo	1. Teve dificuldade de se acalmar quando ficou bravo	1. Had difficulty calming down when mad	1. Had trouble calming down when angry	1. Had difficulty calming down when angry	1. Teve dificuldade de se acalmar quando ficou bravo
2. Become frustrated easily	2. Ficou facilmente frustrado	2. Ficou facilmente frustrado	2. Ficou facilmente frustrado	2. Got easily frustrated	2. Was easily frustrated	2. Was easily frustrated	2. Ficou facilmente frustrado
3. Have a "short fuse" (become angry quickly)	3. Teve "pavio curto" (ficou bravo rapidamente)	3. Teve "pavio curto" (ficou bravo rapidamente)	3. Teve "pavio curto" (ficou bravo rapidamente)	3. Had a short fuse (got easily mad)	3. Was easily irritated	3. Had a short fuse (became angry quickly)	3. Teve "pavio curto" (ficou bravo rapidamente)
4. Yell angrily at someone	4. Gritou enraivecidamente com alguém	4. Gritou raivosamente com alguém	4. Gritou de raiva com alguém	4. Vented anger on someone	4. Shouted angrily at someone	4. Yelled angrily at someone	4. Gritou de raiva com alguém
5. Act irritable	5. Agiu de maneira irritada	5. Agiu de forma irritadiça	5. Agiu de forma irritada	5. Acted angrily	5. acted in as irritable manner	5. Acted irritable	5. Agiu de forma irritada
6. Stay angry for a long time	6. Permaneceu bravo por um longo período	6. Ficou bravo por um longo tempo	6. Ficou bravo por um tempo longo	6. Stayed mad for a long time	6. Was angry for a long time	6. Was angry for a long time	6. Ficou bravo por um tempo longo
7. Have a hot or explosive temper	7. Teve um temperamento esquentado ou explosivo	7. Teve um temperamento esquentado ou explosivo	7. Teve um temperamento esquentado ou explosivo	7. Had a hot temper or a burst of temper	7. had a hot or explosive temper	7. Had a hot or explosive temper	7. Teve um temperamento esquentado ou explosivo

8. Get extremely angry	8. Ficou extremamente bravo	8. Ficou extremamente bravo	8. Ficou extremamente bravo	8. Got extremely mad	21. Was extremely angry	8. Was extremely angry	8. Ficou extremamente bravo
9. Stamp feet or hold breath during a temper tantrum (temper outburst, "fall-out," or melt-down)	9. Bateu o pé ou segurou a respiração durante uma birra (acesso de raiva, briga (“fall-out”), crise (“melt-down’)).	9. Bateu os pés ou segurou a respiração durante um ataque de birra (acesso de raiva, briga ou descontrole)	9. Bateu os pés ou segurou a respiração durante um ataque de birra (acesso de raiva, briga ou descontrole)	9. Stomped his/her feet or hold his/her breath during a temper tantrum (anger spell, fight, decontrol)	9. Stomped his feet or hold his breath during a tantrum (outburst of anger, violence or dyscontrol)	9. Stomped his/her feet or held his/her breath during a temper tantrum (outburst of anger, fight or meltdown)	9. Bateu os pés ou segurou a respiração durante um ataque de raiva
10. Have a temper tantrum (temper outburst, "fall-out," or melt-down) that lasted longer than 5 minutes	10. Apresentou birra (acesso de raiva, briga, crise) que durou mais de 5 minutos	10. Teve um ataque de birra (acesso de raiva, briga ou descontrole) que durou por mais de 5 minutos	10. Teve um ataque de birra (acesso de raiva, briga ou descontrole) que durou por mais de 5 minutos	10. Had a temper tantrum (anger spell, fight, decontrol) that lasted more than 5 minutes	10. Had a tantrum (outburst of anger, violence or dyscontrol) that lasted for more than 5 minutes	10. Had a temper tantrum (outburst of anger, fight or meltdown) that lasted for more than 5 minutes	10. Teve um ataque de raiva que durou por mais de 5 minutos
11. Keep on having a temper tantrum (temper outburst, "fall-out," or melt-down) even when you tried to help him/her calm down	11. Continuou apresentando uma birra (acesso de raiva, briga, crise) mesmo quando você tentou ajudá-lo/la a se acalmar	11. Permaneceu tendo um ataque de birra (acesso de raiva, briga ou descontrole) mesmo quando você tentou acalmar ele ou ela	11. Continuou tendo um ataque de birra (acesso de raiva, briga, descontrole) mesmo quando você tentou ajudá-lo/la a se acalmar?	11. Kept having a temper tantrum (anger spell, fight, decontrol) even when you tried to help him/ her to calm him/her down	11. Kept having a tantrum (outburst of anger, violence or dyscontrol) even when you tried to help he/she calm down	11. Continued having a temper tantrum (outburst of anger, fight or meltdown) even when you attempted to help he/she calm down	11. Continuou tendo um ataque de raiva mesmo quando você tentou ajudá-lo/la a se acalmar
12. Lose temper or have a tantrum with other adults (e.g., babysitter, family member)	12. Perdeu o controle ou apresentou birra com outros adultos (por ex.: babá, familiares)	12. Perdeu a cabeça ou teve um ataque de birra com outros adultos (ex. babá, membro da família)	12. Perdeu a controle ou teve um ataque de birra com outros adultos (ex. babá, membro da família)	12. Lost control or had a temper tantrum with other adults (ex. nanny, family member)	12. Lost control or had a tantrum with other adults (e.g.: nanny, family member)	12. Lost control or had a temper tantrum with other adults (e.g.: babysitter, family member)	12. Perdeu a controle ou teve um ataque de birra com outros adultos (ex. babá, membro da família)
13. Lose temper or have a tantrum with you or other parent	13. Perdeu o controle ou apresentou birra com você ou o pai/a mãe	13. Perdeu a cabeça ou teve um ataque de birra com você ou com o outro progenitor	13. Perdeu o controle ou teve um ataque de birra com você ou com o pai / a mãe	13. Lost control or had a temper tantrum with you or with father/mother	13. Lost control or had a tantrum with you or the father/mother	13. Lost control or had a temper tantrum with you or the father/mother	13. Perdeu o controle ou teve um ataque de raiva com o pai ou com a mãe
14. Lose temper or have a tantrum when frustrated, angry, or upset	14. Perdeu o controle ou apresentou birra quando estava frustrado, bravo ou chateado	14. Perdeu a cabeça ou teve um ataque de birra quando frustrado, bravo ou chateado	14. Perdeu o controle ou teve um ataque de birra quando estava frustrado, bravo ou chateado	14. Lost control or had a temper tantrum when frustrated, mad or upset.	14. Lost control or had a tantrum when frustrated, angry or upset	14. Lost control or had a temper tantrum when frustrated, angry or upset	14. Perdeu o controle ou teve um ataque de birra quando estava frustrado, bravo ou chateado
15. Lose temper or have a tantrum when tired,	15. perdeu o controle ou apresentou birra quando cansado,	15. Perdeu a cabeça ou teve um ataque de birra quando	15. Perdeu o controle ou teve um ataque de birra quando	15. Lost control or had a temper tantrum	15. Lost control or had a tantrum when tired,	15. Lost control or had a tantrum when tired,	15. Perdeu o controle ou teve um ataque de birra quando

hungry, or sick	com fome ou doente	cansado, com fome ou doente	estava cansado, com fome ou doente	when tired, hungry or ill	hungry or sick	hungry or sick	estava cansado, com fome ou doente
16. Lose temper or have tantrum to get something he or she wanted	16. Perdeu o controle ou apresentou birra para conseguir algo que queria	16. Perdeu a cabeça ou teve um ataque de birra para conseguir algo que ele ou ela queria	16. Perdeu o controle ou teve um ataque de birra para conseguir algo que ele ou ela queria	16. Lost control or had a temper tantrum to get something he/she wanted	16. Lost control or had a tantrum to get something that he/she wanted	16. Lost control or had a tantrum to get something that he/she wanted	16. Perdeu o controle ou teve um ataque de birra para conseguir algo que ele ou ela queria
17. Lose temper or have a tantrum during daily routines, such as bedtime, mealtime, or getting dressed	17. Perdeu o controle ou apresentou birra durante rotina diárias, como hora de dormir, das refeições ou de se vestir	17. Perdeu a cabeça ou teve um ataque de birra durante rotinas diárias, como hora de dormir e de comer ou se vestir	17. Perdeu o controle ou teve um ataque de birra durante atividades do dia a dia, como hora de dormir, de comer ou de se vestir	17. Lost control or had a temper tantrum during day by day activities like bed time, meal or dressing time.	17. Lost control or had a tantrum during daily activities, such as bedtime, meals or dressing up	17. Lost control or had a temper tantrum during daily activities, such as bedtime, meals or getting dress	17. Perdeu o controle ou teve um ataque de birra durante atividades do dia a dia, como hora de dormir, de comer ou de se vestir
18. Break or destroy things during a temper tantrum, "fall-out," or melt- down	18. Quebrou ou destruiu coisas durante uma birra, briga ou crise	18. Quebrou ou destruiu coisas durante um ataque de birra, uma briga ou um descontrole	18. Quebrou ou destruiu coisas durante um ataque de birra, uma briga ou um descontrole	18. Broke or destroyed things during a temper tantrum, a fight or a decontrol	18. Broke or destroyed objects during a tantrum, fight or episode of dyscontrol	18. Broke or destroyed objects during a temper tantrum, fight or meltdown	18. Quebrou ou destruiu coisas durante um ataque de raiva
19. Have a temper tantrum (temper outburst, "fall-out," or melt-down)	19. Apresentou birra (acesso de raiva, briga, crise)?	19. Teve um ataque de birra (acesso de raiva, briga ou descontrole)	19. Teve um ataque de birra (acesso de raiva, briga ou descontrole)	19. Had a temper tantrum (anger spell, fight or decontrol)	19. Had a tantrum (outburst of anger, violence or dyscontrol)	19. Had a temper tantrum (outburst of anger, fight or meltdown)	19. Teve um ataque de raiva
20. Have a temper tantrum (temper outburst, "fall-out," or melt-down) until exhausted	20. Apresentou uma birra (acesso de raiva, briga, crise) até ficar exausto?	20. Teve um ataque de birra (acesso de raiva, briga ou descontrole) até cansar	20. Teve um ataque de birra (acesso de raiva, briga ou descontrole) até ficar exausto	20. Had a temper tantrum (anger spell, fight or decontrol) until got exhausted	20. Had a tantrum (outburst of anger, violence or dyscontrol) until getting exhausted	20. Had a temper tantrum (outburst of anger, fight or meltdown) until feeling exhausted	20. Teve um ataque de raiva até ficar exausto
21. Lose temper or have a tantrum "out of the blue" or for no reason	21. Perdeu a paciência ou apresentou birra “do nada” ou sem nenhum motivo	21. Perdeu a cabeça ou teve um ataque de birra repentinamente ou sem razão	21. Perdeu o controle ou teve um ataque de birra “do nada” ou sem nenhum motivo	21. Lost control or had a temper tantrum out of the blue or with no reason	21. Lost control or had a tantrum out of the blue or without any reason	21. Lost control or had a temper tantrum “out of the blue” or without a reason	21. Perdeu o controle ou teve um ataque de birra “do nada” ou sem nenhum motivo
22. Hit, bite, or kick during a tantrum (temper outburst, "fall-out," or melt-down)	22. Bateu, mordeu ou chutou durante uma birra (acesso de raiva, briga, crise)	22. Bateu, mordeu ou chutou durante um ataque de birra (acesso de raiva, briga ou descontrole)	22. Bateu, mordeu ou chutou durante um ataque de birra (acesso de raiva, briga ou descontrole)	22. Hit, bit or kicked out during a temper tantrum (anger spell, fight or decontrol)	22. Hit, bit or kicked during a tantrum (outburst of anger, violence or dyscontrol)	22. Hit, bit or kicked during a tantrum (outburst of anger, fight or meltdown)	22. Bateu, mordeu ou chutou durante um ataque de raiva
Noncompliance	**Desobediência**	**Descumprimento**	**Desobediência**	**Noncompliance**	**Noncompliance**	**Noncompliance**	**Desobediência**
1. Break rules even	1. Quebrou regras	1. Quebrou regras	1. Quebrou regras	1. Broke rules even	1. Broke rules even	1. Broke rules even	1. Quebrou regras

when he or she knew you were watching	mesmo quando ele ou ela sabia que você estava observando	mesmo quando ele/ela sabia que você estava vendo	mesmo quando ele ou ela sabia que você estava vendo	when he knew you were watching	when he/she knew you were observing	when he/she knew you were watching	mesmo quando ele ou ela sabia que você estava vendo
2. Argue when asked to do something	2. Discutiu quando lhe foi pedido para fazer algo	2. Discutiu quando alguém pediu para ele/ela fazer algo	2. Discutiu quando foi solicitado que ele/ela fizesse algo	2. Argued when asked to do something	2. Argued when he/she was asked to do something	2. Argued when he/she was asked to do something	2. Discutiu quando foi solicitado que ele/ela fizesse algo
3. Act stubborn	3. Agiu com teimosia	3. Agiu com teimosia	3. Agiu com teimosia	3. Acted with stubbornness	3.Acted stubbornly	3. Acted stubborn	3. Agiu com teimosia
4. Say “no” when told to do something	4. Disse “não” quando lhe foi dito para fazer algo	4. Disse “não” quando falaram para ele/ela fazer algo	4. Disse “não” quando foi solicitado que ele/ela fizesse algo	4. Said no when asked to do something	4. Said “no” when he/she was asked to do something	4. Said “no” when he/she was asked to do something	4. Disse “não” quando foi solicitado que ele/ela fizesse algo
5. Act sassy, talk back, or have a “smart mouth”	5. Agiu de forma audaciosa, respondeu com petulância ou teve “língua afiada”	5. Agiu de forma atrevida, retrucou ou teve uma “língua afiada”	5. Agiu de forma atrevida, retrucou ou teve uma “língua afiada”	5. Acted boldly, replied or had a sharp tongue	5. Acted daringly, retorted or had a “sharp tongue”	5. Acted sassy, talked back or had a “sharp mouth”	5. Agiu de forma atrevida, retrucou ou foi rude ou desrespeitoso
6. Ignore directions	6. Ignorou instruções	6. Ignorou instruções	6. Ignorou instruções	6. Ignored instructions	6. Ignored Instructions	6. Ignored instructions	6. Ignorou instruções
7. Do exactly what you just said not to do	7. Fez exatamente o que você disse para não fazer	7. Fez exatamente o que você disse para não fazer	7. Fez exatamente o que você disse para não fazer	7. Did exactly what you told not to do	7. Did exactly what you told him not to do	7. Did exactly what you said not to do	7. Fez exatamente o que você acabou de dizer para não fazer
8. Refuse to follow directions	8. Recusou-se a seguir instruções	8. Recusou-se a seguir instruções	8. Recusou-se a seguir instruções	8. Refused to follow instructions	8. Refused to follow instructions	8. Refused to follow instructions	8. Recusou-se a seguir instruções
9. Disobey or break rules with you or other parent	9. Desobedeceu ou quebrou regras com você ou com o pai/a mãe	9. Quebrou regras ou desobedeceu a você ou ao outro progenitor	9. Quebrou regras ou desobedeceu a você ou ao pai / à mãe	9. Broke rules or disobeyed you or his father or mother	9. Broke rules or disobeyed you or his father/mother	9. Broke rules or disobeyed you or his father/mother	9. Quebrou regras ou desobedeceu a você ou ao pai / à mãe
10. Disobey or break rules with other adults (e.g., babysitter, family member)	10. Desobedeceu ou quebrou regras com outros adultos (por exemplo: babá, membro da família)	10. Quebrou regras ou desobedeceu outros adultos (ex. babá, membro da família)	10. Quebrou regras ou desobedeceu a outros adultos (ex. babá, membro da família)	10. Broke rules or disobeyed other adults (ex. nanny, family member)	10. Broke rules or disobeyed other adults (e.g., nanny, family member)	10. Broke rules with or disobeyed other adults (e.g.: Babysitter, family member)	10. Quebrou regras ou desobedeceu a outros adultos (ex. babá, membro da família)
11. Disobey or break rules for no reason or “out of the blue”	11. Desobedeceu ou quebrou regras sem motivo ou “do nada”	11. Quebrou regras ou desobedeceu sem razão ou repentinamente	11. Quebrou regras ou desobedeceu sem nenhum motivo ou “do nada”	11. Broke rules or disobeyed without no reason or out of the blue	11. Broke rules or disobeyed without any reason or “out of the blue“	11. Broke rules or disobeyed without a reason or “out of the blue“	11. Quebrou regras ou desobedeceu sem nenhum motivo ou “do nada”
12. Disobey or break rules when tired, hungry or sick	12. Desobedeceu ou quebrou regras quando	12. Quebrou regras ou desobedeceu quando cansado,	12. Quebrou regras ou desobedeceu quando estava cansado,	12. Broke rules or disobeyed when tired, hungry, or ill	12. Broke rules or disobeyed when was tired, hungry or sick	12. Broke rules or disobeyed when tired, hungry or sick	12. Quebrou regras ou desobedeceu quando estava cansado,

	cansado, com fome ou doente	com fome ou doente	com fome ou doente				com fome ou doente
13. Disobey or break rules when frustrated, angry or upset	13. Desobedeceu ou quebrou regras quando frustrado, bravo ou chateado	13. Quebrou regras ou desobedeceu quando frustrado, bravo ou chateado	13. Quebrou regras ou desobedeceu quando estava frustrado bravo ou chateado	13. Broke rules or disobeyed when frustrated or upset	13. Broke rules or disobeyed when was frustrated, angry or upset	13. Broke rules or disobeyed when frustrated, angry or upset	13. Quebrou regras ou desobedeceu quando estava frustrado bravo ou chateado
14. Disobey or break rules to get something s/he wanted	14. Desobedeceu ou quebrou regras para conseguir algo que ele/ela queria	14. Quebrou regras ou desobedeceu para obter algo que ele ou ela queria	14. Quebrou regras ou desobedeceu para obter algo que ele/ela queria	14. Broke rules or disobeyed to get something that he/she wanted	14. Broke rules or disobeyed to obtain something he/she wanted	14. Broke rules or disobeyed to obtain something he/she wanted	14. Quebrou regras ou desobedeceu para obter algo que ele/ela queria
15. Disobey or break rules during daily routines, such as bedtime, mealtime, or getting dressed	15. Desobedeceu ou quebrou regras durante rotinas diárias, como hora de dormir, das refeições ou de se vestir	15. Quebrou regras ou desobedeceu durante rotinas diárias, como hora de dormir e comer ou se vestir	15. Quebrou regras ou desobedeceu durante rotinas diárias, como hora de dormir, de comer, ou de se vestir	15. Broke rules or disobeyed during daily routines, like bed time, eating time or dressing time	15. Broke rules or disobeyed during daily activities, such as bedtime, meals or dressing up	15. Broke rules or disobeyed during daily activities, such as bedtime, meals or getting dressed.	15. Quebrou regras ou desobedeceu durante rotinas diárias, como hora de dormir, de comer, ou de se vestir
16. Not do what you asked no matter what	16. Não fez o que você pediu, não importando o que	16. Não fez o que você pediu independentemente das consequências	16. Não fez o que você pediu independentemente do que acontecesse ou das consequências	16. Didn't do what you asked regardless of what would happen or of the consequences	16. Did not do what you asked, regardless of the outcomes or consequences	16. Did not do what you asked, no matter what	16. Não fez o que você pediu independentemente do que acontecesse ou das consequências
17. Argue about "just about anything"	17. Discutiu "por qualquer coisa"	17. Discutiu sobre praticamente tudo	17. Discutiu "por qualquer coisa"	17. Argued for anything	17. Argued for no reason	17. Argued about anything	17. Discutiu bastante, mesmo que por coisas pequenas
18. Automatically resist whatever you ask	18. Resistiu automaticamente, independente do que você pediu	18. Automaticamente resistiu independentemente do que você pediu	18. Se opôs a fazer qualquer coisa automaticamente independente do que você pediu?	18. Opposed automatically to do anything no matter what you asked	18. Opposed automatically to do anything, regardless of what you would ask	18. Automatically resisted, no matter what you asked	18, automaticamente se opôs a qualquer coisa que você pediu
19. Take things s/he was not allowed to have	19. Pegou coisas que ele ou ela não tinha permissão para ter	19. Pegou coisas que ele/ela não tinha permissão para ter	19. Pegou coisas que ele/ela não tinha permissão para ter	19. Got things he/she wasn't allowed to have	19. Took things he/she was not allowed to have	19. Took things he or she was not allowed to have	19. Pegou coisas que ele/ela não tinha permissão para ter
20. Show off or laugh while misbehaving	20. Exibiu-se ou deu risada enquanto se comportava mal	20. Riu ou ficou se mostrando enquanto se comportava mal	20. Ficou se mostrando ou riu enquanto se comportava mal	20. Was showing off or laughing when misbehaving	20. Kept showing off or laughed while misbehaving	20. Kept showing off or laughed while misbehaving	20. Ficou se mostrando ou riu enquanto se comportava mal
21. Do risky things s/he	21. Fez coisas	21. Fez coisas	21. Fez coisas	21. Did risky things that	21. Did risky things that	21. Did risky things	21. Fez coisas

knew were not allowed	arriscadas que ele/ela sabia que não lhe era permitido	arriscadas que ele/ela sabia que eram proibidas	arriscadas que ele/ela sabia que não eram permitidas	he/she knew weren't allowed	he/she did know were not allowed	he/she knew were not allowed	arriscadas que ele/ela sabia que não eram permitidas
22. Misbehave in ways that were dangerous or unsafe	22. Comportou-se mal de uma forma que era arriscada ou perigosa	22. Comportou-se mal de formas perigosas ou que não eram seguras	22. Comportou-se mal de formas perigosas ou que não eram seguras	22. Misbehaved in dangerous ways or in unsafe ones	22. Misbehaved or behaved in dangerous or unsafe ways	22. Misbehave in ways that were dangerous or unsafe	22. Comportou-se mal de formas perigosas ou que não eram seguras
Aggression	**Agressão**	**Agressão**	**Agressão**	**Aggression**	**Aggression**	**Aggression**	**Agressão**
1. Act aggressively when frustrated, angry, or upset	1. Agiu agressivamente quando frustrado, bravo ou chateado	1. Agiu agressivamente quando frustrado, bravo ou chateado	1. Agiu agressivamente quando estava frustrado(a), bravo(a) ou chateado(a)	1. Acted aggressively when frustrated, mad or upset.	1. Acted aggressively when frustrated, angry or upset	1. Act aggressively when frustrated, angry or upset	1. Agiu agressivamente quando estava frustrado(a), bravo(a) ou chateado(a)
2. Act aggressively to try to get something s/he wanted	2. Agiu agressivamente para tentar conseguir algo que ele/ela queria	2. Agiu agressivamente para tentar obter algo que ele/ela queria	2. Agiu agressivamente para tentar conseguir algo que ele/ela queria	2. Acted aggressively to try to get something that he/she wanted	2. Acted aggressively to try to get something that he/she wanted	2. Act aggressively to try to get something he/she wanted	2. Agiu agressivamente para tentar conseguir algo que ele/ela queria
3. Act aggressively with you or other parent	3. Agiu agressivamente contra você ou com o pai/a mãe	3. Agiu agressivamente contra você ou contra o outro progenitor	3. Agiu agressivamente contra você ou contra o pai/ a mãe	3. Acted aggressively against you or against his father or mother	3. Acted aggressively against you or his/her mother/father	3. Act aggressively with you or father/mother	3. Agiu agressivamente contra você ou contra o pai/ a mãe
4. Act aggressively "out of the blue" or for no reason	4. Agiu agressivamente "do nada", sem motivo	4. Agiu agressivamente repentinamente ou sem razão	4. Agiu agressivamente "do nada" ou sem nenhum motivo	4. Acted aggressively out of the blue or with no reason	4. Acted aggressively "out of the blue" or without any reason	4. Act aggressively "out of the blue" or for no reason	4. Agiu agressivamente "do nada" ou sem nenhum motivo
5. Act aggressively with other adults (e.g., babysitter, family member)	5. Agiu agressivamente contra outros adultos (por exemplo: babá, familiares)	5. Agiu agressivamente contra outros adultos (ex. babá, membro da família)	5. Agiu agressivamente contra outros adultos (ex. babá, membro da família)	5. Acted aggressively against other adults (ex. nanny, Family member)	5. Acted aggressively against other adults (e.g.: nanny, family member)	5. Act aggressively against other adults (e.g.: babysitter, family member)	5. Agiu agressivamente contra outros adultos (ex. babá, membro da família)
6. Act aggressively towards other children (not including brother or sister)	6. Agiu agressivamente contra outras crianças (sem incluir irmãos ou irmãs)	6. Agiu agressivamente contra outras crianças (sem incluir irmão e irmã)	6. Agiu agressivamente contra outras crianças (sem incluir irmão e irmã)	6. Acted aggressively against other kids (not including brother or sister)	6. Acted aggressively against other kids (excluding brothers and sisters)	6. Acted aggressively against other kids (excluding brothers and sisters)	6. Agiu agressivamente contra outras crianças (sem incluir irmão e irmã)
7. Throw something at someone (not as part of a game)	7. Atirou coisas em alguém (sem ser como parte de um jogo)	7. Jogou algo em alguém (sem ser parte de um jogo)	7. Jogou algo em alguém (sem ser parte de um jogo)	7. Threw something at someone (without it being part of a game)	7. Threw something at someone (without being part of a game)	7. Threw something at someone (not as part of a game)	7. Jogou algo em alguém (sem ser parte de um jogo)
8. Try to hurt someone to get back at them	8. Tentou machucar alguém para se vingar	8. Tentou machucar ou magoar alguém para se vingar da pessoa	8. Tentou machucar ou magoar alguém para se vingar	8. Tried to hurt or hurt someone's feelings to get revenge	8. Tried to hurt or upset someone for revenge	8. Tried to hurt or upset someone out of revenge	8. Tentou machucar ou magoar alguém para se vingar

9. Break or ruin things on purpose	9. Quebrou ou destruiu coisas de propósito	9. Quebrou ou estragou coisas de propósito	9. Quebrou ou estragou coisas de propósito	9. Broke or botched things on purpose	9. Broke or ruined objects on purpose	9. Broke or ruined objects on purpose	9. Quebrou ou estragou coisas de propósito
10. Hurt someone on purpose	10. Machucou alguém de propósito	10. Machucou ou magoou alguém de propósito	10. Machucou ou magoou alguém de propósito	10. Harmed or hurt someone on purpose	10. Hurt or upset someone on purpose	10. Harmed or hurt someone on purpose	10. Machucou ou magoou alguém de propósito
11. Curse at someone	11. Amaldiçoou alguém	11. Xingou alguém	11. Xingou alguém	11. Swore someone	11. Cursed someone	11. Cursed at someone	11. Praguejou, usou palavras rudes ou ofensivas para expressar raiva em relação a alguém
12. Bully someone	12. Praticou bullying em alguém	12. Fez bullying com alguém	12. Fez bullying em alguém	12. Bullied someone	12. Bullied someone	12. Bullied someone	12. Fez bullying em alguém
13. Hit, shove, or kick you or other parent	13. Bateu, empurrou ou chutou você ou o pai/ a mãe	13. Bateu, chutou ou empurrou você ou o outro progenitor	13. Bateu, chutou ou empurrou você ou o pai/ a mãe	13. Hit, kicked or shoved you or his/her father/mother	13. Hit, kicked or pushed you or his/her father/mother	13. Hit, kicked or shoved you or his/her father/mother	13. Bateu, chutou ou empurrou você ou o pai/ a mãe
14. Hit, shove, or kick other adults (not including parents)	14. Bateu, empurrou ou chutou outros adultos (sem incluir os pais)	14. Bateu, chutou ou empurrou outros adultos (sem incluir os pais)	14. Bateu, chutou ou empurrou outros adultos (sem incluir os pais)	14. Bit, kicked or shoved other adults (not including parents)	14. Hit, kicked or pushed other adults (excluding his parents)	14. Hit, kicked or shoved other adults (not including parents)	14. Bateu, chutou ou empurrou outros adultos (sem incluir os pais)
15. Hit, shove, or kick other children	15. Bateu, empurrou ou chutou outras crianças	15. Bateu, chutou ou empurrou outras crianças quando ninguém podia ver	15. Bateu, chutou ou empurrou outras crianças	15. Bit, kicked or shoved other kids	15. Hit, kicked or pushed other kids	15. Hit, kicked or shoved other children	15. Bateu, chutou ou empurrou outras crianças
16. Hit someone with an object	16. Bateu em outra pessoa com um objeto	16. Bateu em alguém com um objeto	16. Bateu em alguém com um objeto	16. Bit someone with an object	16. Hit someone with an object	16. Hit someone with an object	16. Bateu em alguém com um objeto
17. Do or say mean or “not nice” things to other children	17. Fez ou falou coisas malvadas ou “não legais” para outra criança	17. Disse ou fez coisas más ou “não agradáveis” para outras crianças	17. Fez ou disse coisas más ou “não agradáveis” para outras crianças	17. Did or said bad or not pleasant things to other kids	17. Did or said mean or unpleasant things to other kids	17. Did or said mean or “not nice” things to other children	17. Fez ou disse coisas más ou “não agradáveis” para outras crianças
18. Get into fights	18. Entrou em brigas	18. Entrou em brigas	18. Entrou em brigas	18. Got in many fights	18. Got into fights	18. Got into fights	18. Entrou em brigas
19. Call another child names	19. Xingou outras crianças	19. Chamou outras crianças de “nomes feios” ou palavrões	19. Chamou outras crianças de “nomes feios” ou palavrões	19. Called other kids with ugly names or bad language	19. Called other kids “ugly names” or swore	19. Called children “bad names” or curse words	19. Chamou outras crianças de “nomes feios” ou palavrões
20. Pinch, scratch, or pull someone’s hair	20. Beliscou, arranhou ou puxou o cabelo de alguém	20. Beliscou, arranhou ou puxou o cabelo de alguém	20. Beliscou, arranhou ou puxou o cabelo de alguém	20. Pinched, scratched or pulled someone’s hair	20. Pinched, scratched or pulled someone’s hair	20. Pinched, scratched or pulled someone’s hair	20. Beliscou, arranhou ou puxou o cabelo de alguém
21. Say or do mean or “not nice” things to other	21. Falou ou fez coisas malvadas ou “não legais” para outras	21. Disse ou fez coisas más ou “não agradáveis” para outras	21. Disse ou fez coisas más ou “não agradáveis” para outras	21. Told or did bad or not pleasant things to other kids	21. Said or did mean or unpleasant things to other kids	21. Said or did mean or unpleasant things to other	21. Disse ou fez coisas más ou “não agradáveis” para outras

children behind their backs	crianças, “por trás das costas”	crianças pelas costas	crianças “pelas costas”	behind their back		children behind their back	crianças “pelas costas”
22. Tell others not to let someone play with them	22. Falou para outros não deixarem alguém brincar com eles	22. Disse para outros não deixarem alguém brincar com eles	22. Disse para outros não deixarem alguém brincar com eles	22. Told others not to let someone play with them	22. Told others not to let someone play with them	22. Told others not to let someone play with them	22. Disse para outros não deixarem alguém brincar com eles
23. Refuse to let other children play with him/her	23. Recusou-se a deixar outras crianças brincarem com ele/ela	23. Recusou a deixar outras crianças brincar com ele/ela	23. Recusou-se a deixar que outras crianças brincassem com ele/ela	23. Refused to let other kids play with him/her	23. Refused to let other kids play with him/her	23. Refused to let other children play with him/her	23. Recusou-se a deixar que outras crianças brincassem com ele/ela
24. Threaten someone	24. Ameaçou alguém	24. Ameaçou alguém	24. Ameaçou alguém	24. Threatened someone	24. Threatened someone	24. Threatened someone.	24. Ameaçou alguém
25. Spit at someone	25. Cuspiu em alguém	25. Cuspiu em alguém	25. Cuspiu em alguém	25. Spit at someone	25. Spat on someone	25. Spit at someone	25. Cuspiu em alguém
Punishment Insensitivity	**Insensibilidade à punição**	**Insensibilidade à punição**	**Insensibilidade à punição**	**Insensitivity to punishment**	**Insensitivity to punishment**	**Punishment Insensitivity**	**Insensibilidade à punição**
1. Deny he or she did something that was not allowed	1. Negou que ele ou ela havia feito algo que não lhe era permitido	1. Negou que ele/ela fez algo que não era permitido	1. Negou que ele ou ela fez algo que não era permitido	1. Denied that he/she did something that wasn’t allowed	1. Denied that he or she did something that was not allowed	1. Denied that he/she did something that was not allowed	1. Negou que ele ou ela fez algo que não era permitido
2. Keep on misbehaving no matter what you do	2. Continuou se comportando mal independente do que você fez	2. Continuou se comportando mal “independentemente do que você fizesse"	2. Continuou se comportando mal “independentemente do que você fizesse"	2. Kept misbehaving regardless of what you would do	2. Kept misbehaving regardless what you did	2. Kept misbehaving no matter what you did	2. Continuou se comportando mal “independentemente do que você fizesse"
3. Act like s/he did not know right from wrong	3. Agiu como se ela/ele não soubesse distinguir certo do errado	3. Agiu como se ele/ela não soubesse diferenciar o certo do errado	3. Agiu como se ele/ela não soubesse diferenciar o certo do errado	3. Acted as if he/she didn’t know to tell right from wrong	3. Acted as if he/she did not know how to distinguish right from wrong	3. Acted like if he/she did not know right from wrong	3. Agiu como se ele/ela não soubesse diferenciar o certo do errado
4. Not care when punished	4. Não se importou quando foi punido	4. Não se importou quando foi punido	4. Não se importou quando foi punido	4. Didn’t care when was punished	4. Did not care when was punished	4. Did not care when punished	4. Não se importou quando foi punido
5. Act like rules didn’t matter	5. Agiu como se as regras não tivessem importância	5. Agiu como se regras não importassem	5. Agiu como se regras não importassem	5. Acted as if the rules didn’t mind	5. Acted as if rules did not matter	5. Acted like rules did not matter	5. Agiu como se regras não importassem
6. Act like he or she didn’t hear you when you said no	6. Agiu como se ele ou ela não tivesse escutado quando você disse não	6. Agiu como se ele ou ela não tivesse ouvido quando você disse “não”	6. agiu como se ele ou ela não tivesse escutado quando você disse não?	6. Acted as if he/she hadn’t listened when you said no	6. Acted as if he or she did not listen when you said “no	6. Acted like he/she did not hear you when you said “no”	6. agiu como se ele ou ela não tivesse escutado quando você disse não?
7. Refuse to apologize	7. Recusou-se a pedir desculpas	7. Recusou-se a pedir desculpas	7. Recusou-se a pedir desculpas	7. Refused to apologize	7. Refused to apologize	7. Refused to apologize	7. Recusou-se a pedir desculpas

10 ANEXOS

10.1 Anexo 1: Termo de consentimento livre e esclarecido do ‘Estudo Mappa’

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO- HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO
Versão IV - Junho de 2016

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .....

DOCUMENTO DE IDENTIDADE Nº: ..... SEXO: M □ F □

DATA NASCIMENTO: ..... / ..... / .....

ENDEREÇO: ..... Nº..... APTO: .....

BAIRRO: ..... CIDADE: .....

CEP: ..... TELEFONE: DDD (.....) ...../CELULAR:.....

2. RESPONSÁVEL LEGAL: .....

NATUREZA (grau de parentesco, tutor, curador etc.): .....

DOCUMENTO DE IDENTIDADE Nº: ..... SEXO: M □ F □

DATA NASCIMENTO: ..... / ..... / .....

ENDEREÇO: ..... Nº..... APTO: .....

BAIRRO: ..... CIDADE: .....

CEP: ..... TELEFONE: DDD (.....) ...../CELULAR:.....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA: **"Ensaio clínico controlado randomizado comparando metilfenidato a treinamento parental no tratamento de crianças pré-escolares com transtorno de déficit de atenção/hiperatividade".**

Pesquisador Responsável: Guilherme Vanoni Polanczyk.

Cargo/Função: Professor Doutor

Inscrição no Conselho Regional: Nº 142725 - CRM -SP

Unidade do HCFMUSP: Departamento de Psiquiatria

2. Investigadores Executantes:

Débora Muszkat Salviani
Inscrição no Conselho Regional: Nº136259- CRM - SP

Erika Mendonça de Morais
Inscrição no Conselho Regional: Nº 124933 – CRM – SP

Giovana Del Prette
Inscrição no Conselho Regional: Nº 77732 – CRP - SP

Jordana Verano de Oliveira
Inscrição do Conselho Regional: Nº. 171338 – CRM - SP

Luisa Shuguemi Sugaya
Inscrição no Conselho Regional: Nº 150791 – CRM – SP

3. Avaliação do Risco da Pesquisa

RISCO MÍNIMO RISCO MÉDIO **X**

RISCO BAIXO RISCO MAIOR

4. **Duração da Pesquisa**: 24 meses

1. Justificativa e objetivos: Você está sendo convidado(a) como voluntário(a) para participar, juntamente com seu filho(a), de um estudo sobre problemas de atenção, impulsividade e hiperatividade na infância. Este estudo tem como objetivo ajudar os médicos a conhecer melhor as crianças que apresentam desatenção, impulsividade e/ou hiperatividade, chamado transtorno de déficit de atenção e hiperatividade ou TDAH. Além disso, este estudo irá testar e comparar dois tipos de tratamento, um com medicação e outro com orientação aos pais.

2. **Procedimentos:** Se você concordar em participar desde estudo, juntamente com seu filho(a), vocês irão participar de uma triagem para avaliarmos se seu filho possui os critérios necessários para ser incluído no estudo, que são: apresentar diagnóstico de TDAH (de acordo com critérios do DSM-5), apresentar pontuação no SNAP – IV acima de 32, apresentar pontuação igual ou maior que 70 na avaliação do QI e ter um responsável legal com capacidade de compreender os objetivos e instruções do estudo e responder algumas questões sobre seus sentimentos e comportamentos no dia a dia e a forma como sua família se relaciona, quando vierem ao Instituto de Psiquiatria para consultas. A avaliação com você será em um único dia com duração de aproximadamente 1 hora e meia, com seu filho(a) será dividida em 2 dias, com duração aproximada de 1 hora e meia em cada dia. Também solicitaremos que o professor(a) do seu filho responda um questionário sobre o comportamento dele na escola. Se identificarmos que seu filho(a) tem diagnóstico de Transtorno de Déficit de Atenção e Hiperatividade e preenche os demais critérios citados acima, vocês serão convidados a fazer parte de um dos grupos de tratamento deste estudo. Este estudo é duplo cego, ou seja, nem você nem os membros da equipe, a não ser o pesquisador responsável, irá saber em qual grupo você e seu filho estão participando. Os grupos são: 1) medicamentoso (metilfenidato) e informações educacionais; 2) orientações educacionais e medicamento placebo, e 3) informações educacionais e placebo. Caso ocorra alguma intercorrência, revelaremos imediatamente o grupo de tratamento do qual o seu filho (a) faz parte. Após o período de estudo, os participantes poderão ser acompanhados no ambulatório do Programa de Diagnóstico e Intervenções Precoces (PRODIP) do Instituto de Psiquiatria HCFMUSP. Para avaliarmos melhor seu filho (a) faremos uma ressonância magnética e uma ultrassonografia transcraniana (uma "fotografia" do cérebro), e filmaremos uma brincadeira sua com ele. Essas imagens serão utilizadas apenas para o fim desta pesquisa e não serão tornadas públicas. Você seu filho (a) e o pai dele (a) também serão convidados a participar de procedimentos de coleta de sangue e seu filho (a) irá fazer um eletrocardiograma (que avalia a atividade elétrica do coração). É possível que você se sinta cansada ou constrangida por ter que responder coisas sobre aspectos emocionais, mas estará sempre acompanhada por psiquiatra e psicólogo treinados que farão esforço para deixá-la confortável. Os procedimentos oferecem riscos médios como detalhado abaixo.

A seleção para participação em qualquer um dos três grupos será por sorteio, sendo:

a) **metilfenidato e informações educacionais**: seu filho(a) será tratado com Metilfenidato por 8 semanas, durante este período ele será acompanhado por um psiquiatra da infância e adolescência, responsável por ajustar a dose e avaliar como está tolerando à medicação. Você, juntamente com o pai e/ou mãe de seu filho (a) e ele(a) participarão de sessões semanais, com duração de 1 hora e meia, de informação educacionais importantes para a educação das crianças.

b) **orientações educacionais e tratamento com placebo:** serão realizadas em 8 sessões semanais com duração de 1 hora e meia cada, tem por objetivo orientar os pais na educação de seu filho(a), aumentando a competência e confiança dos pais e melhorando a relação entre pais e filhos. Seu filho receberá, durante este período, um tratamento com medicamento placebo.

c) **informações educacionais e tratamento com placebo**: serão realizadas sessões semanais, com 1 hora e meia de duração de informação educacionais importantes para a educação das crianças e tratamento com placebo por 8 semanas, após este período seu filho (a) encaminhado(a) para acompanhamento no Ambulatório do Programa de Diagnóstico e Intervenções Precoces – PRODIP- do Instituto de Psiquiatria HCFMUSP.

Como serão realizados os procedimentos rotineiros:

Coleta de sangue e/ou saliva (mãe, pai e filho(a)): O sangue será coletado através de pulsão venosa, em 2 tubos de 5 ml. Sua saliva e do pai de seu filho(a) será coletada através de um frasco. A coleta da saliva de seu filho (a) será feita através de um tipo de cotonete. Você e o pai de seu filho (a) fornecerão amostra de sangue e/ou saliva uma única vez durante o estudo. Seu filho(a) fornecerá amostras por duas vezes, no início e ao final do estudo.

Procedimento Crowell: iremos avaliar sua relação com seu filho(a) através da filmagem de uma brincadeira livre entre vocês, entre 35 a 60 minutos. Essa filmagem será utilizada apenas para os fins desta pesquisa.

Exame de ressonância magnética: poderemos fazer, no início e no final do estudo, um exame de Ressonância Magnética em seu filho (a), que é uma "fotografia" do cérebro. Esse exame não é prejudicial a seu filho/a, não tem radiação e não precisa de medicação. Antes da realização do exame, faremos um treino com psicólogos treinados para aclimatar a criança ao ambiente da ressonância (sons e equipamentos) e treinar sua habilidade de ficar parada durante a coleta do exame.

Ultrassonografia transcraniana: iremos fazer, no início e ao final do estudo, um exame de ultrassonografia transcraniana em seu filho(a) , que também é uma "fotografia" do cérebro. Esse exame não é prejudicial a seu filho (a), não produz dor, radiação e não precisa de sedação. A duração do exame é em torno de 30 minutos. Você poderá permanecer com seu filho durante todo o período, com ele sentado em seu colo.

Eletrocardiograma - ECG: será realizado no início e ao final do estudo, ele é uma "fotografia" do coração. A coleta do registro eletrocardiográfico será realizada através de eletrodos de superfície não invasiva e adequada para esta faixa etária. A duração é no máximo de 5 minutos e será realizado com o seu filho (a) acordado (a).

Tratamento com Placebo: o placebo é uma substância sem nenhuma propriedade farmacológica, ou seja, não tem efeito. Usaremos como substância placebo amido de milho, que será administrada para seu filho durante o período de 8 semanas, sem nenhum prejuízo ou risco para a saúde de seu filho. Ao final das 8 semanas, você e o médico saberão se este foi o tratamento sorteado.

Quebra do cegamento dos pais: O cegamento dos pais sobre qual grupo experimental seu filho está participando ocorrerá imediatamente, caso ocorra qualquer relato de intercorrência com seu filho durante o período do estudo em que o conhecimento sobre o uso de metilfenidato seja clinicamente importante.

Informação Educacional: serão abordados temas importantes para a educação das crianças.

Esses procedimentos serão realizados no Instituto de Psiquiatria da FMUSP com profissional especializado. A qualquer momento você poderá decidir se quer ou não receber o resultado dos exames realizados. Deixamos claro que os exames solicitados têm finalidade de pesquisa e não têm significado clínico definido, não sendo possível, a partir de nosso conhecimento atual, definir o diagnóstico de uma doença ou forma de tratamento através desses exames. Além disso, deixamos claro que se você e seu filho optarem por não oferecer sangue ou saliva, ou por não realizarem o exame de ressonância magnética ou ultrassom, vocês poderão ainda participar nas outras etapas do estudo.

Riscos e Desconfortos:

a) Coleta de amostra de sangue. Neste procedimento pode ocorrer o aparecimento de manchas arroxeadas no local de onde o sangue foi tirado. Todos os participantes serão previamente orientados com relação a este risco e sobre os cuidados necessários caso ocorra. Além disso, raramente o local de onde foi retirada amostra de sangue pode inflamar e necessitar de cuidados locais (limpeza e pomadas) por alguns dias. Exames de sangue são necessários para investigar alguns genes que podem influenciar a resposta ao tratamento e os efeitos colaterais.

b) Coleta de saliva: Não há riscos físicos envolvidos. Pode gerar angústia ou ansiedade para aqueles que considerem o procedimento desagradável.

c) Ressonância Magnética de Crânio: Durante o exame o único desconforto é um ruído intermitente e o fato de estar em um ambiente fechado. No entanto para amenizar o desconforto, será fornecido tapa-ouvidos. O exame pode gerar angústia ou ansiedade, pois durante o procedimento é solicitado que a criança permaneça imóvel dentro da máquina. Para amenizar este possível desconforto, o pesquisador executante estará presente durante o exame e conversará com seu filho(a) nos intervalos entre as coletas de imagem. Uma das vantagens da RM é o fato de não utilizar radiações, portanto, não existem efeitos nocivos.

d) Ultrassonografia transcraniana: A ultrassonografia não é invasiva e não tem efeitos colaterais, é realizada com as crianças acordadas, não precisando de sedação. Durante o exame pode ocorrer desconforto pela aplicação de gel frio na cabeça, que será limpo imediatamente após o termino do exame. Este gel não tem cheiro, não tem cor, não causa alergia e é removível com água.

e) Eletrocardiograma: não oferece risco a seu filho(a) por ser um exame não invasivo e indolor. As crianças serão avaliadas acordadas. Não há necessidade de sedação. Não há risco de choque ou de passagens de corrente elétrica.

f) Preenchimento dos questionários: os participantes podem ficar cansados com o preenchimento dos questionários, já que leva mais ou menos uma hora para responder todas as perguntas. Também podem se sentir ansiosos por responderem perguntas sobre os próprios sentimentos e comportamentos no dia a dia. Para diminuir o cansaço utilizaremos avaliadores treinados e instrumentos curtos.

g) Orientações educacionais: você pode se sentir ansioso (a) e desconfortável ao discutir questões pessoais sobre o relacionamento com seu filho (a) na presença do outro pai/mãe e do psicólogo que coordenará o grupo.

h) Tratamento com medicação: o seu filho (a) poderá apresentar efeitos reação ao uso do metilfenidato, que pode incluir dor de cabeça, dor de barriga, aumento de agitação e dificuldade para pegar no sono. Estas reações geralmente melhoram após alguns dias de tratamento. Seu filho (a) será acompanhado por psiquiatra da infância e adolescência, que avaliará a presença e gravidade das reações, se necessário a dose da medicação será ajustada ou o tratamento será interrompido.

i) Informações educacionais e placebo: seu filho (a) irá permanecer sem tratamento por período de 8 semanas de duração do estudo, apresentando sintomas e prejuízos relacionados ao TDAH, no entanto, todos as crianças serão avaliadas por psiquiatra infantil durante o estudo em casos de piora significativa dos sintomas clínicos, a criança será retirada do estudo e encaminhada para tratamento clínico. Seus dados serão considerados até o momento em que permaneceram no estudo. Não há nenhum risco relacionado ao uso de placebo medicamentoso, que será amido de milho.

Potenciais benefícios: Os principais benefícios deste estudo são a identificação precoce de problema mentais, possibilitada pela avaliação de saúde mental, e a instituição mais rápida do tratamento. Além disso, os resultados deste estudo poderão influenciar como os médicos indicam o tratamento para o transtorno de déficit de atenção/hiperatividade; beneficiando seu filho(a) e outras crianças que apresentem o transtorno, representando um potencial benefício para a sociedade. O uso de um grupo controle se justifica, pois não há tratamento considerado de primeira escolha para TDAH em pré- escolar e irá possibilitar que um maior número de pacientes, que estariam em uma lista de espera demorada, dada escassez de serviços especializados em saúde mental para essa faixa etária na rede pública, tenha acesso ao tratamento clínico em ambulatório especializado na FMUSP.

Garantia de acesso à informação: Em qualquer etapa do estudo você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é o Dr. Guilherme Polanczyk, que pode ser encontrado no Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da USP, Rua Dr. Ovídio Pires de Campos, 785, 1º andar. Telefone (11) 2661- 7594. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com a Comissão de Ética para Análises de Projetos de Pesquisa – CAPPesq) – Rua Dr. Ovídio Pires de Campos, 225 - 5º andar, telefones 2661-6442 ramais 16,17 e 18 ou 2661-7585. E-mail: cappesq.adm@hc.fm.usp.br

Não participar ou interromper participação: Você tem liberdade para se recusar a participar ou retirar seu consentimento, e deixar de participar em qualquer fase do estudo, sem penalização alguma e sem prejuízo do cuidado que seu filho(a) recebe neste serviço.

Outras informações e sigilo: O armazenamento e arquivamento dos dados colhidos (seus e de sua família) incluindo os genéticos, que serão utilizados de acordo com hipóteses do presente estudo e outras informadas pela literatura, desde que seja aprovado pelo CEP e pela CONEP e que se busque contato para autorização futura. As informações produzidas neste estudo serão mantidas em lugar seguro, codificadas e a identificação só poderá ser realizada pelo pessoal envolvido diretamente com o projeto. Caso o material venha a ser utilizado para publicação científica ou atividades didáticas, não serão utilizados nomes que possam vir a identificá-los. Suas informações e de sua família são totalmente sigilosas, só os componentes da equipe da pesquisa terão acesso a elas. Vocês têm direito de serem mantidos atualizados sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores;

Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo realização de exames e consultas. Também não há compensação financeira relacionada à sua participação e de sua família. Suas despesas com deslocamento serão parcialmente compensadas pela pesquisa.

Direito a assistência em caso de intercorrências e durante o estudo: durante todo o estudo e após o seu término você poderá comunicar e pedir assistência por danos diretos relacionados ao estudo, ficando a sua disposição a pesquisador responsável Dr. Guilherme Polanczyk, pelo telefone (11) 2661-7594 para qualquer eventualidade. Seu filho (a) terá garantida a continuidade do tratamento, após a conclusão do estudo, se assim estiver indicado, no ambulatório PRODIP na FMUSP.

Compromisso utilização dos dados: Os dados obtidos somente serão usados para o fim previsto neste projeto de pesquisa e qualquer outro uso terá que se solicitar o seu consentimento.

Acredito ter sido suficientemente informado a respeito do processo de seleção para participação no estudo, estando ciente que, se após a avaliação inicial, meu filho (a) não apresentar os critérios necessários para inclusão, ele não poderá participar do estudo. Preenchendo os critérios de inclusão, ele (a) será sorteado para participar de um dos três grupos do estudo. Não tenho dúvidas sobre as informações que li ou que foram lidas para mim, descrevendo o estudo.

"Ensaio clínico controlado randomizado comparando metilfenidato a treinamento parental no tratamento de crianças pré-escolares com transtorno de déficit de atenção/hiperatividade"

Eu discuti com o **Dr. Guilherme V. Polanczyk** sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que a minha participação e de meu filho (a) é isenta de despesas e que tenho garantia do acesso a tratamento quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Número de Seleção: _____

Número de Inclusão no Estudo (Randomização): _____

Recebi uma cópia datada e assinada deste documento (Termo de Consentimento Livre e Esclarecido)

_____ Data:_____/____/_____

Assinatura do Representante Legal (mãe)

_____ Data:_____/____/_____

Assinatura do Representante Legal (pai)

_____ Data:_____/____/_____

Assinatura da Testemunha (somente para casos de menores de

18 anos, analfabetos, semi-analfabetos ou portadores de

deficiência auditiva ou visual)

(Somente para o responsável do projeto)

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

_____ Data:_____/____/_____

Assinatura do Responsável pelo estudo

10.2 Anexo 2: *Affective Reactivity Index* (ARI – P)

(LEIA) *Agora nós vamos falar sobre seu filho. Por favor, responda as perguntas pensando em com seu filho é normalmente, como se comporta,* ***sempre comparando com outras crianças da mesma idade que ele, na maior parte do tempo e não apenas uma vez ou outra.*** *Lembre-se: cada afirmação deve descrever o comportamento e os sentimentos dele, com maior frequência, nos* ***últimos 6 meses.*** ***Apresente a pista visual no2.***

	NÃO É VERDADE	**UM POUCO VERDADE**	**CERTAMENTE VERDADE**
1. É incomodado facilmente por outras pessoas			
2. Perde a calma frequentemente			
3. Fica irritado (a) por muito tempo.			
4. Está irritado (a) na maior parte do tempo			
5. Irrita-se frequentemente.			
6. Perde a calma facilmente.			
7. De modo geral, a *irritabilidade* causa problemas a ele (a).			

10.3 Anexo 3: *Multidimensional Assessment Profile – Disruptive Behavior* (MAP-DB)

Agora eu vou comentar algumas situações e gostaria que você me respondesse com que frequência seu filho as realiza. As opções de resposta são:

Nunca	Raramente (Menos de 1 vez por semana)	Alguns dias (1-3 dias na semana)	A maior parte dos dias (4-6 dias na semana)	Todos os dias da semana	Várias vezes por dia
1	2	3	4	5	6

Pouca preocupação com os outros	**1**	**2**	**3**	**4**	**5**	**6**
1. Continuou fazendo algo que estava assustando ou chateando alguém						
2. Agiu como se ele/ela não se importasse quando outra pessoa se sentia mal ou triste						
3. Gostou de deixar os outros bravos						
4. Pareceu não se importar com os sentimentos de outros adultos (por ex.: babá, membros da família)						
5. Pareceu não se importar com os seus sentimentos ou com os sentimentos do pai ou da mãe						
6. Agiu como se ele/ela não se importasse quando alguém estava bravo ou chateado						
7. Fez coisas para humilhar ou envergonhar outros						
8. Agiu como se ele/ela não se importasse em agradar outras pessoas						
9. Não se importou com os sentimentos dos outros, quando estava frustrado, bravo ou chateado						
Descontrole emocional						
1. Teve dificuldade de se acalmar quando ficou bravo						
2. Ficou frustrado facilmente						
3. Teve “pavio curto” (ficou bravo rapidamente)						
4. Gritou raivosamente com alguém						
5. Agiu de forma irritada						
6. Ficou bravo por um tempo longo						
7. Teve um temperamento esquentado ou explosivo						
8. Ficou extremamente bravo						

9. Bateu os pés ou segurou a respiração durante um ataque de raiva						
10. Teve um ataque de raiva que durou por mais de 5 minutos						
11. Continuou tendo um ataque de raiva mesmo quando você tentou ajudá-lo/la a se acalmar?						
12. Perdeu a controle ou teve um ataque de birra com outros adultos (ex. babá, membro da família)						
13. Perdeu o controle ou teve um ataque de birra com você ou com o pai / a mãe						
14. Perdeu o controle ou teve um ataque de birra quando estava frustrado, bravo ou chateado						
15. Perdeu o controle ou teve um ataque de birra quando estava cansado, com fome ou doente						
16. Perdeu o controle ou teve um ataque de birra para conseguir algo que ele ou ela queria						
17. Perdeu o controle ou teve um ataque de birra durante rotinas diárias, como hora de dormir, de comer ou de se vestir						
18. Quebrou ou destruiu coisas durante um ataque de raiva						
19. Teve um ataque de raiva						
20. Teve um ataque de raiva até ficar exausto						
21. Perdeu o controle ou teve um ataque de birra “do nada” ou sem nenhum motivo						
22. Bateu, mordeu ou chutou durante um ataque de raiva						
Desobediência						
1. Quebrou regras mesmo quando ele ou ela sabia que você estava vendo						
2. Discutiu quando foi solicitado que ele/ela fizesse algo						
3. Agiu com teimosia						
4. Disse “não” quando foi solicitado que ele/ela fizesse algo						
5. Agiu de forma atrevida, retrucou ou teve uma “língua afiada”						
6. Ignorou instruções						
7. Fez exatamente o que você disse para não fazer						
8. Recusou-se a seguir instruções						
9. Quebrou regras ou desobedeceu a você ou ao pai / à mãe						
10. Quebrou regras ou desobedeceu a outros adultos (ex. babá, membro da família)						
11. Quebrou regras ou desobedeceu sem nenhum motivo ou “do nada”						

12. Quebrou regras ou desobedeceu quando estava cansado, com fome ou doente						
13. Quebrou regras ou desobedeceu quando estava frustrado bravo ou chateado						
14. Quebrou regras ou desobedeceu para obter algo que ele/ela queria						
15. Quebrou regras ou desobedeceu durante rotinas diárias, como hora de dormir, de comer, ou de se vestir?						
16. Não fez o que você pediu independentemente do que acontecesse ou das consequências						
17. Discutiu “por qualquer coisa”						
18. Resistiu automaticamente independentemente do que você pediu						
19. Pegou coisas que ele/ela não tinha permissão para ter						
20. Ficou se mostrando ou riu enquanto se comportava mal						
21. Fez coisas arriscadas que ele/ela sabia que não eram permitidas						
22. Comportou-se mal de formas perigosas ou que não eram seguras						
Comportamento agressivo						
1. Agiu agressivamente quando estava frustrado bravo ou chateado						
2. Agiu agressivamente para tentar obter algo que ele/ela queria						
3. Agiu agressivamente contra você ou contra o pai/ a mãe						
4. Agiu agressivamente “do nada” ou sem nenhum motivo						
5. Agiu agressivamente contra outros adultos (ex. babá, membro da família)						
6. Agiu agressivamente contra outras crianças (sem incluir irmão e irmã)						
7. Jogou algo em alguém (sem ser parte de um jogo)						
8. Tentou machucar ou magoar alguém para se vingar						
9. Quebrou ou estragou coisas de propósito						
10. Machucou ou magoou alguém de propósito						
11. Xingou alguém						
12. Fez bullying em alguém						
13. Bateu, chutou ou empurrou você ou o pai/ a mãe						
14. Bateu, chutou ou empurrou outros adultos (sem incluir os pais)						
15. Bateu, chutou ou empurrou outras crianças						
10. Bateu em alguém com um objeto						

11. Fez ou disse coisas más ou “não agradáveis” para outras crianças						
12. Entrou em brigas						
13. Chamou outras crianças de “nomes feios” ou palavrões						
14. Beliscou, arranhou ou puxou o cabelo de alguém						
15. Disse ou fez coisas más ou “não agradáveis” para outras crianças “pelas das costas”						
16. Disse para outros não deixarem alguém brincar com eles						
11. Recusou-se a deixar que outras crianças brincassem com ele/ela						
12. Ameaçou alguém						
13. Cuspiu em alguém						
Insensibilidade à punição						
1. Negou que ele ou ela fez algo que não era permitido						
2. Continuou se comportando mal “independentemente do que você fizesse"						
3. Agiu como se ele/ela não soubesse diferenciar o certo do errado						
4. Não se importou quando foi punido						
5. Agiu como se regras não importassem						
6. Agiu como se ele ou ela não tivesse escutado quando você disse não						
7. Recusou-se a pedir desculpas						