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Vertessen, K.; Luman, M.; Bet, P.; Bergwerff, C.E.; Bottelier, M.; Stoffelsen, R.; ... ; Oosterlaan, J.

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ORIGINAL RESEARCH ARTICLE

Improving Methylphenidate Titration in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): A Randomized Controlled Trial Using Placebo-Controlled Titration Implemented in Clinical Practice

Karen Vertessen[1,2] · Marjolein Luman[1,3] · Pierre Bet[4] · Catharina E. Bergwerff[5] · Marco Bottelier[6] · Reino Stoffelsen[3] · James M. Swanson[7] · Annemiek Wisse[8] · Jos Twisk[9] · Jaap Oosterlaan[1,10,11]

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Abstract

Background and Objectives Concerns exist regarding the rising use of methylphenidate. A double-blind, placebo-controlled methylphenidate titration (PCT) for children with attention-deficit/hyperactivity disorder (ADHD) has shown potential to improve titration (i.e., detection of placebo responders and larger ADHD symptom improvement) in experimental settings. This study aims to determine if these advantages can be transferred to clinical settings.

Method Children (aged 5–13 years) with an ADHD diagnosis and an indication to start methylphenidate (MPH) treatment were recruited. Participants were randomized to PCT or care as usual (CAU) in a 1:1 ratio followed by a 7-week randomized controlled trial (T1) and 6-month, naturalistic, open-label follow-up (T2). Parents, teachers, and physicians rated ADHD symptoms, ADHD medication use, MPH dosing, and treatment satisfaction using questionnaires.

Results A total of 100 children were enrolled and randomized to PCT ($n = 49$) or CAU ($n = 51$). In the PCT group, we found 8.2% placebo responders, 16.3% non-responders, and 65.3% responders to MPH. With PCT compared with CAU, a significantly larger number of children discontinued MPH (T1: 24.5 vs 5.9%, $p = 0.009$; T2: 41.7 vs 10.4%, $p < 0.001$) and refrained from using other pharmacological treatment (T1: 20.4 vs 3.9%, $p = 0.013$; T2: 20.83 vs 6.25%, $p = 0.002$). At both timepoints, there were no significant differences between the groups in the average dose of MPH, ADHD symptoms, or treatment satisfaction.

Conclusions PCT can be used to improve detection of children who do not benefit from MPH, and may therefore potentially reduce overtreatment of ADHD with MPH.

1 Introduction

Attention-deficit hyperactivity disorder (ADHD) affects around 5% of school-age children worldwide [1] and is associated with significant impairments in several functional domains and a reduction in quality of life [2, 3]. It is a highly complex and heterogeneous disorder in terms of its multifactorial etiological risk factors, symptom presentation, and comorbid problems [2, 4].

Methylphenidate (MPH) is a first-line pharmacological treatment for children with ADHD [5, 6]. The effectiveness of MPH in reducing the core symptoms of ADHD (inattention and/or hyperactivity/impulsivity), has been well documented in randomized controlled trials, with effect sizes close to 1.0 [7]. MPH is reasonably well tolerated, with mostly mild side effects, such as reduced appetite and delayed sleep onset [7, 8].

The clinical use of MPH to treat children with ADHD involves several issues. First, clinical guidelines [5, 6] recommend the use of 'stepwise titration' to determine the optimal therapeutic dose. This entails that treatment starts with a low dose, which is gradually increased until the most effective dose with acceptable side effects is reached [5, 6]. While research shows that higher doses lead to better symptom control at the group level, higher doses do not always lead to better symptom control at the individual level [9–12]. These findings are in line with recent conclusions from Farhat et al. [13] that MPH titration should include a wide range of different doses. Second, stepwise titration does not offer a comparison of MPH with placebo, while

Extended author information available on the last page of the article

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Key Points

Placebo-controlled titration shows that around 30% of children with attention-deficit/hyperactivity disorder (ADHD) do not benefit from methylphenidate compared to placebo.

In the placebo-controlled titration group, fewer children continued using methylphenidate and overall ADHD medication.

Despite the reduced usage of medication in the placebo-controlled titration group, ADHD symptoms did not differ statistically from those in the care-as-usual group.

Implementing a placebo-controlled titration method can enhance the identification of children who do not benefit from methylphenidate, potentially curbing the overprescription of methylphenidate for ADHD within clinical practice.

placebo-controlled titration in an experimental setting classified 13% of children as placebo responders after titration [9], indicating no additional beneficial effects of MPH over placebo. Thus, if titration does not involve a comparison between the active dose and placebo, placebo responders may likely remain undetected and will be exposed to MPH side effects, without taking benefit of the use of MPH. Third, ADHD symptoms typically vary depending on the context and setting [14, 15]. Therefore, optimal titration should include standardized assessment of treatment outcomes and tolerability (e.g., using questionnaires and/or semi-structured interviews) using multiple informants (typically parents and teachers, or the child themself in case of children aged > 12 years), covering multiple contexts [5, 16–18]. However, titration in clinical practice is usually based on reports by only one informant and standardized assessment of treatment outcomes is often lacking [19].

In earlier attempts to optimize MPH titration in clinical practice, an optimized titration protocol has been developed by Coghill and Seth [17]. The titration protocol involved a structured dose-optimization procedure, including stepwise increase of MPH doses and standardized assessment of treatment outcomes. The implementation of this protocol has led to larger ADHD symptom improvement [17]. However, the titration protocol did not address a key issue in MPH titration: placebo response.

A method that addresses placebo response and was part of the Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA) study protocol [18], is double-blind, placebo-controlled titration (PCT). In PCT, different doses of MPH and placebo are prescribed double-blind and in random order, and the effect of each dose is systematically assessed with multiple informants in terms of symptom reduction and side effects. Subsequently, it can be determined whether the child is a non-responder, placebo responder, or responder. For responders to MPH, the optimal dose is determined from the dose that provides the most optimal symptom control with minimal side effects. Despite its promising sensitivity to detect non-responders and placebo responders and its ability to objectively determine optimal doses, thus far no studies have directly compared stepwise titration and PCT. Hence, currently, the use of PCT in clinical practice is limited and its use is not recommended in (inter)national guidelines [19].

A titration protocol that allows detection of non-responders and placebo responders would facilitate a swift switch to other interventions to treat ADHD, either pharmacological, including stimulants [20], or non-pharmacological, including a revision of the indication for pharmacological treatment. By optimizing pharmacological treatment of ADHD in a relatively brief period of time, treatment adherence may be enhanced, and long-term outcomes may be improved [21].

To address the gap in clinical PCT studies, we developed a PCT protocol based on the titration protocol used in the MTA study [14], modified to improve clinical usability. To increase practical use, weekly instead of daily dose changes are used, similarly to Luman et al. [22] and others [23–25]. A supportive application was built into an online tool to assess ADHD symptoms and side effects weekly using online questionnaires that are automatically send out, and to generate an advisory report to guide physicians in their decision on MPH treatment.

The current study aimed to investigate the effectiveness and feasibility of our newly developed PCT method (hereafter referred to as PCT) when embedded in clinical practice for children with ADHD aged 5–13 years and compared with stepwise titration (i.e., care as usual [CAU]). This way, the study was aimed at determining whether the advantages of PCT seen in experimental settings (detection of placebo responders, larger ADHD symptom improvement), would transfer to clinical settings. Results may inform clinical guidelines on pharmacological treatment of children with ADHD. We hypothesized that PCT as compared with CAU would lead to more optimal treatment effects (i.e., better symptom control and a lower rate of children continuing MPH treatment after titration) because of the potential of PCT to detect non-responders and placebo responders. Additionally, we explored parents' and physicians' satisfaction with the two titration methods. Further, we studied to what extent results of the PCT on usefulness of MPH treatment and dosing were adopted by physicians, to assess the clinical use of the PCT procedure.

2 Method

2.1 Trial Design

The current study used a 7-week randomized controlled trial and a 6-month naturalistic, open-label follow-up. After screening (T0), participants were randomized to PCT or CAU titration in a 1:1 ratio for 7 weeks, with outcome assessment immediately following titration (T1) and 6 months after titration (T2). The local ethics committee approved the study (METC Amsterdam UMC, 2016.594) and the study was registered prospectively in the Dutch trial register (NL8121).

2.2 Participants

Children were recruited from 13 mental health clinics in The Netherlands between May 2017 and December 2019. Inclusion criteria were (i) a clinical diagnosis of ADHD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) [2], (ii) 5–13 years of age, (iii) Intelligence Quotient (IQ) > 70, (iv) indication for MPH treatment, as determined by the treating physician, and (v) no pharmacological treatment for ADHD for a period of at least 4 weeks prior to study entry, to avoid transfer of medication effects. Comorbid diagnoses were not an exclusion criterion. Diagnostic status was confirmed by the first author, a trained child psychiatrist, using (1) the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS), a semi-structured, standardized, investigator-based parent interview, with a good internal reliability and high validity [26, 27] and (2) the teacher-rated Disruptive Behavior Disorder rating scale (DBDRS), with a sufficient internal reliability and good validity assessing the presence and severity of symptoms of ADHD [28]. The diagnosis was confirmed, according to DSM-5 classification of ADHD, when there were at least six out of nine symptoms of inattention and/or hyperactivity-impulsivity, observed in multiple settings, which interfere with functioning or development.

2.3 Titration Methods

2.3.1 Placebo-Controlled Titration (PCT)

The PCT protocol was based on the titration protocol used in the Multimodal Treatment of ADHD study (MTA study) [12] and modified to improve clinical usability by (1) adding a lead-in phase to determine if all doses used during titration were tolerated in terms of side effects, (2) weekly instead of daily dose changes to increase feasibility [22, 25], and (3) the use of an online tool to assess treatment outcomes. All participants received PCT medication schedules consisting of the following treatment conditions: placebo and 5, 10, 15 and 20 mg of MPH administered twice daily, with the latter dose only used in children > 25 kg, limiting the maximum dose to 1 mg/kg/day [25]. The titration procedure started with a lead-in phase [25] (not blinded), consisting of 4 days in which all three (5, 10, 15 mg) or four (20 mg in children > 25 kg) doses were administered in ascending order. The sequence of the MPH doses was randomly determined (see Sect. 2.6) with the restriction that the highest dose was never the starting dose or the dose administered after placebo. This was done to reduce possible side effects due to sudden large dose augmentation. Duration of the PCT was 3–5 weeks, depending on the child's weight and MPH doses tolerated. During PCT, treatment with a particular dose started on a Saturday and was administered for 7 consecutive days, twice daily, at breakfast (around 8 a.m.) and at lunch time (around 12 a.m.).

2.3.2 Care as Usual (Stepwise Titration)

For the CAU, limited guidelines were provided to the participating physicians. To prevent the comparison between the PCT and CAU being cofounded by the use of different MPH formulations (modified release, different composition, etc.), physicians were instructed to (i) prescribe immediate-release MPH tablets provided by the study pharmacy, (ii) use a twice-daily dosing regimen, according to the current guidelines and standard clinical practice for this age group in the Netherlands, and (iii) use stepwise titration, as currently advised by international guidelines [5, 6, 16]. Stepwise titration starts with a low dose and dose is gradually increased within the 10 mg to 60 mg daily dose range (maximum dose < 1 mg/kg/day), until the child shows optimal symptom reduction with mild side effects that are acceptable for the child and parents. This method does not include a separate lead-in phase. The method to increase dose, evaluate symptoms and side effects, and the definition of optimal symptom reduction and acceptable side effects were determined by the physicians. Hence, CAU may vary between participating children, which is in accordance with care as usual.

2.3.3 Supportive Application

The titration procedure was standardized using a tailor-made application built into an existing, and clinically widely used, online tool [29]. Using this tool, questionnaires were sent out automatically to both parents and teachers at the end of each titration week. Daily reminders were sent out automatically, if required. An algorithm built into the online tool used the Reliable Change Index to determine improvement in SWAN

(Strength and Weakness of ADHD symptoms and Normal Behavior Rating Scale) scores collected at baseline and for placebo and each of the active doses. This was done for both parent and teacher ratings separately. Based on these results combined with the parent- and teacher-rated side effects, the algorithm classified participants as non-responders, placebo responders, or responders. For responders, the algorithm also determined optimal dose. For a more detailed description of the algorithm, see the electronic supplementary material (ESM). Physicians were encouraged to discuss the results of the titration and the recommendation with parents and children and use these results for shared decision making on further medication treatment and dosing. Physicians were allowed to deviate from the recommendations generated by the algorithm on the usefulness of MPH treatment and dosing.

2.4 Follow-Up

The 7-week, randomized controlled trial was followed by a 6-month, naturalistic, open-label follow-up phase. MPH was no longer provided by the study pharmacy. The type of pharmacological treatment used was left to the physician's discretion and could involve any type of MPH formulation available in the Netherlands. The study protocol allowed continuing immediate-release MPH, switching to modified-release MPH or any other medication that may be used to treat ADHD, or discontinue pharmacological treatment.

2.5 Outcome Measures

Outcomes were measured using questionnaires sent out through the online tool, in both treatment groups at baseline prior to randomization (T0), after the 7-week titration period (T1), and at a 6-month follow-up (T2).

2.5.1 MPH Use and Adherence to Results of PCT

Physicians and parents reported on medication use, including the dosing regimen used at T1 and T2. Physician-reported information was the preferred source of information, unless the child was no longer under the care of the physician who started MPH treatment ($n = 51$ at T2), in which case parent-reported information was used (only at T2). These data were used to determine (i) the number of children discontinuing treatment with MPH, (ii) the number of children discontinuing treatment with any ADHD medication, and (iii) the mean total daily dose of MPH taken by children continuing MPH treatment.

2.5.2 ADHD Symptoms

ADHD symptom severity was measured with the SWAN [30], completed by parents and teachers at T0, T1, and T2. The SWAN is an 18-item rating scale measuring the presence and severity of ADHD symptoms on a continuum (from strength to difficulty). Items are rated on a 7-point Likert scale ranging from − 3 (far above average) to + 3 (far below average). This approach allows reports with larger variability in scores (with the possibility to score items as a strength), in contrast to the scoring in other commonly used questionnaires like the SNAP (Swanson, Nolan and Pelham Teacher and Parent Rating Scale; from normal behavior to difficulty) [30, 31]. The SWAN usually requires informants to base their ratings on observations of the child's behavior during the past month. For the current study, ratings pertained to the past week. The total scores of both the parent- and the teacher-reported scales were used as outcome measures. In addition, an average total score was calculated across parent and teacher ratings, further referred to as the combined parent + teacher score. The SWAN has shown high internal reliability (0.94–0.96) and validity [30, 31].

2.5.3 Satisfaction with Titration Method

Parents and physicians were asked to report satisfaction with the titration method using a custom-made questionnaire (available in the ESM) at T1 and T2.

2.6 Study Procedure

Clinicians from the participating clinics informed parents and children of the study. The first author provided parents and children who were interested in participating with additional (written) information on the study. Parents and children older than 11 years provided signed informed consent. The physician delivered a prescription to the academic pharmacy, where randomization to one of the two titration groups (PCT or CAU) took place. Children assigned to the PCT group were then randomized to one of the medication schedules. Thereafter, parents received the study medication required for the entire titration period. Demographic information and outcomes were assessed through questionnaires administered via the online tool. Parents were instructed to contact the treating physician in case of severe side effects or other problems.

2.7 Blinding and Randomization

Randomization tables were used to assign children to one of two titration groups and to determine the exact medication schedule for those children assigned to PCT. Randomization tables were generated using a computerized random number

generator (http://www.randomization.com). Randomization was done by trained staff members from the academic pharmacy, who had no contact with participants. The physician, parents, and children were not blinded for titration method as the two titration methods involved different procedures for titration from the physicians and participants. For children assigned to CAU, tablets of immediate-release MPH 10 mg were dispensed by the academic pharmacy. The dosing schedules in the PCT were blinded for the treating physician, parents, children, and teachers until the end of the titration period. For both study groups, all placebo and MPH tablets were specifically produced by Tiofarma (Oud-Beijerland, The Netherlands, license 2165-F) for this study under European Union Good Manufacturing Practice annex 13 guidelines and were identical in color and shape.

2.8 Statistical Analyses

Data were analyzed on an intention-to-treat basis. Chi-squared or Fisher's exact tests were used to compare groups on demographic variables. The medication use reported at T1 was compared with the advice provided by the algorithm to determine adherence to the advice.

2.8.1 Effects of Titration Methods

The effects of both titration methods were compared at two time points—after the 7-week titration period (T1) and at a 6-month follow-up (T2)—on five outcomes measures using Fisher's exact tests for (1) number of children discontinuing treatment with MPH and (2) number of children discontinuing the use of any ADHD medication. Multilevel analyses (mixed model analysis) were conducted in Stata (version 16) to compare titration methods on (3) mean total daily dose MPH taken (for children continuing MPH), (4) ADHD symptoms (parent, teacher, and combined parent + teacher score), and (5) satisfaction with titration method (parent and physician score). With a sample size of 100 participants, we were powered to detect a difference between both groups with an effect size (with a p-level of 5% [$\alpha = 0.05$], a power of 80% [$1 - \beta = 0.80$], and two-tailed testing) in the order of $d = 0.30$ (small) in difference in the number of children continuing treatment with MPH and an effect size in order of $d = 0.60$ (medium) for the difference in ADHD symptom improvement. Four hierarchical levels were distinguished in the multilevel analyses: observations (Level 1), nested within children (Level 2), nested in physicians (Level 3), and nested in centers (Level 4). Random intercepts at physician and center level were only included if significantly improving model fit as determined by the likelihood ratio test. The models included the group variable (CAU vs PCT), time (T1 vs T2), and the interaction between group and time. The latter was added to estimate the difference between the groups at the different time points. Baseline scores (T0) of the analyzed ADHD symptom outcome were added to the model as a covariate, in order to adjust for possible differences between children in ADHD symptoms at baseline. Missing data were not imputed as longitudinal multilevel analyses adequately deal with missing data [32, 33].

3 Results

3.1 Sample

A total of 100 children with ADHD, aged 5–13 years, were referred for medication treatment and included in the study. Children were recruited from 13 youth mental health clinics across the Netherlands and a total of 41 clinicians participated in the study. Table 1 displays the demographics of the sample. Children in the two groups did not differ significantly on any of the demographic variables ($p > 0.150$), except on age ($p = 0.035$), with the PCT group being older. Age has been found to be associated with the response to MPH, with older children showing weaker responses [34, 35]. Therefore, age was included as a covariate in all analyses.

3.2 Medication and Dose Advice Derived From the PCT

Of 49 subjects assigned to PCT, four (8.2%) stopped PCT during the lead-in phase due to side effects. The remaining 45 subjects (91.2%) successfully completed titration; for two (4.1%) children a dose was not tolerated during the lead-in phase, and was excluded from the PCT. According to individual dose–response graphs, four (8.2% of 49) children did not respond differently to placebo and any of the tested MPH doses and were considered placebo responders. Eight (16.3% of 49) children showed minimal or no improvements during any of the MPH doses compared with baseline, and were considered non-responders to MPH. A total of 32 children (65.3% of 49) responded favorably to at least one of the MPH titration doses compared with baseline: six children (12.24% of 49) to 5 mg/dose, 14 (28.57%) to 10 mg/dose, six (12.24%) to 15 mg/dose, and six (12.24%) to 20 mg/dose. One patient had excessive side effects during PCT at all tested MPH doses, even though this child did well in the lead-in phase. This child discontinued use of MPH (Fig. 1).

3.3 Adherence to the Advisory Report

Prescriptions followed the recommendations as provided by the PCT algorithm on the usefulness of MPH treatment and dosing in 55.1% of the cases. Of the remaining 44.9%

Table 1 Group characteristics

Characteristics	CAU ($n = 51$)	PCT ($n = 49$)	Group comparisons
Age in years, mean (SD)	8.98 (1.35)	9.64 (1.73)	$F(2,98) = -0.66$, $p = 0.035$
Sex, *n* (%) boys	39 (76.47)	31 (63.27)	$\chi^2 = 2.08$, $p = 0.150$
Weight in kg, mean (SD)	33.11 (8.95)	34.11 (10.20)	$F(2,91) = -1$, $p = 0.616$
Autism spectrum diagnosis, *n* (%)	4 (8%)	4 (8%)	Fischer's exact = 1, $p = 0.620$
K-SADS, mean (SD)			
Inattention symptoms	6.71 (1.78)	6.85 (1.94)	$F(2,98) = -0.15$, $p = 0.685$
Hyperactivity-impulsivity symptoms	5.76 (2.20)	5.57 (2.47)	$F(2,98) = 0.19$, $p = 0.680$
ODD symptoms	1.78 (1.90)	2.14 (2.36)	$F(2,98) = -0.36$, $p = 0.404$
SWAN[a], mean (SD)			
Teacher	− 23.78 (12.36)	− 26.45 (11.02)	$F(2,98) = 2.66$, $p = 0.259$
Parent	− 23.82 (12.64)	− 20.80 (13.46)	$F(2,98) = -1.81$, $p = 0.923$
Combined parent + teacher	− 23.80 (9.82)	− 23.62 (8.78)	$F(2,98) = -0.36$, $p = 0.404$
CBCL internalizing problems, mean (SD)	− 23.80 (9.82)	10.5 (7.44)	$F(2,95) = -0.11$, $p = 0.943$
TRF internalizing problems, mean (SD)	7.77 (7.21)	8.07 (6.94)	$F(2,88) = -0.30$, $p = 0.841$

Chi-squared or Fisher's exact tests were used to compare groups on demographic variables. Values are mean ± standard deviation or *n* (%)

ADHD attention-deficit hyperactivity disorder, *CAU* care as usual, *CBCL* Child Behavior Checklist, *K-SADS* Kiddie–Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version, *ODD* oppositional defiant disorder, *PCT* placebo-controlled titration, *SWAN* Strength and Weakness of ADHD symptoms and Normal Behavior Rating Scale, TRF Teachers Report Form

[a]SWAN scores may range between − 27 and 27; combined parent + teacher score: mean total score for parent + teacher ratings

not following the recommendations, one child (4.55%) started using MPH after dropout of the PCT due to side effects, one child (4.55%) defined as a placebo responder continued MPH, six children (27.27%) assessed as non-responders continued using MPH, three children (13.64%) identified as MPH responders discontinued MPH and 11 children (50%) assessed as MPH responders, were prescribed a different, on average lower dose then advised by the algorithm (mean daily doses 18.21 and 23.56 mg, respectively).

3.4 Medication Use

Figure 2 presents medication use in the two titration groups at the two time points. Children in the PCT more often discontinued MPH use compared with the CAU, both at T1 (after titration; 24.5 and 5.9%, respectively; Fischer's exact: $p = 0.009$) and at T2 (6-month follow-up; 41.7 and 10.4%; Fischer's exact: $p < 0.001$). Children in the PCT more often discontinued using any medication for ADHD compared with the CAU group, both at T1 (20.4 and 3.9%, respectively; Fischer's exact: $p = 0.013$) and at T2 (20.83 and 6.25%, respectively; Fischer's exact: $p = 0.002$). There was no significant difference in the mean total daily dose of MPH taken for children continuing MPH treatment after the PCT compared with the CAU at T1 (22.5 mg and 22.8 mg, respectively; $B = -0.35$, SE = 2.04, $p = 0.865$) and at T2 (26.7 mg and 22.17 mg, respectively; $B = 4.07$, SE = 2.60, $p = 0.117$).

3.5 ADHD Symptoms

Figure 3 and Table 2 depict the course of ADHD symptoms from T0 to T2 as measured by the parent-rated, teacher-rated, and combined parent + teacher SWAN score. Based on the intention-to-treat analyses (including all children, also those who discontinued the use of MPH and/or switched to other medication), there were no significant differences between the two titration methods at T1 (adjusting for ratings at T0) for parent-rated symptoms ($B = 1.60$, SE = 2.63, $p = 0.544$), teacher-rated symptoms ($B = -0.72$, SE = 2.82, $p = 0.798$) and the combined parent + teacher score SWAN score ($B = 0.66$, SE = 2.11, $p = 0.753$). Likewise, there were no significant differences between the two titration methods at T2 for parent-rated symptoms ($B = -3.52$, SE = 2.71, $p = 0.194$), teacher-rated symptoms ($B = -4.32$ SE = 2.88, $p = 0.134$) and the combined parent + teacher SWAN score ($B = -3.68$, SE = 2.18, $p = 0.091$). Additionally, we repeated all analyses (i) with SWAN scores converted to a maximum item score of 0 (comparable to the SNAP) [30] and (ii) excluding children that did not follow the recommendations generated by the algorithm on the usefulness of MPH treatment and dosing ($n = 22$), with the results for both additional analyses remaining unchanged (data available from the author upon request).

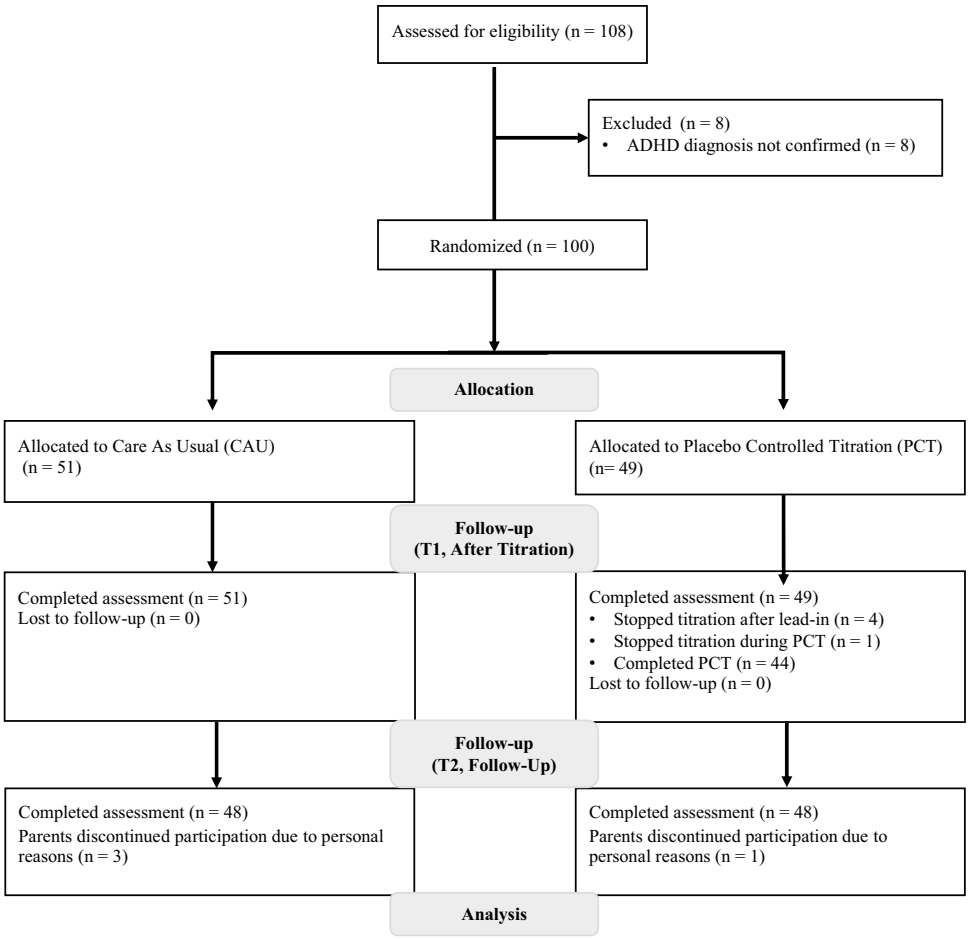

Fig. 1 CONSORT flowchart of participants
ADHD attention-deficit/hyperactivity disorder, *CAU* care as usual, *MPH* methylphenidate, *PCT* placebo-controlled titration, *SWAN* Strength and Weakness of ADHD symptoms and Normal Behavior Rating Scale

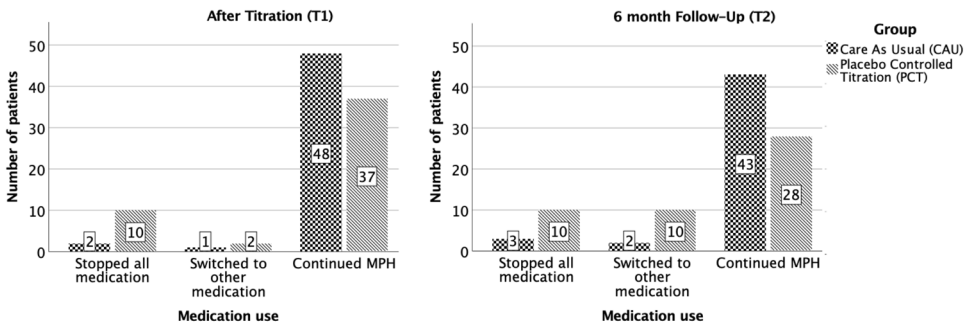

Fig. 2 Medication use after titration and at 6-month follow-up
ADHD attention-deficit/hyperactivity disorder, *CAU* care as usual, *MPH* methylphenidate, *PCT* placebo-controlled titration, *SWAN* Strength and Weakness of ADHD symptoms and Normal Behavior Rating Scale

3.6 Satisfaction

Table 3 depicts the parent- and physician-reported satisfaction rates for both titration methods. There were no significant differences in the satisfaction rates between the two titration methods at T1 for parents ($B = 0.07$, SE = 2.32, $p = 0.977$) and physicians ($B = 0.07$, SE = 2.32, $p = 0.977$) or at T2 for parents ($B = -0.54$, SE = 2.20, $p = 0.804$) and physicians ($B = -0.38$, SE = 2.11, $p = 0.857$).

4 Discussion

This randomized controlled trial investigated whether PCT embedded in clinical practice compared with CAU may result in more optimal use of MPH in children with ADHD. Compared with CAU, PCT resulted in a larger number of children discontinuing MPH, and more children discontinuing any ADHD medication both immediately following titration and at 6-month follow-up. There were no significant differences between the PCT and CAU

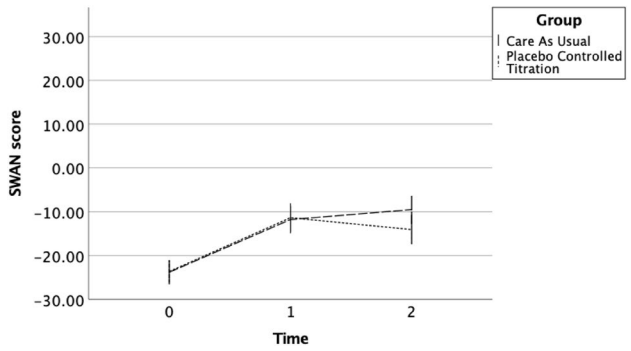

Fig. 3 ADHD symptoms over time in the two titration groups (intention to treat analyses)
Note: Combined parent + teacher SWAN scores are depicted. Error bars represent 95% confidence interval. *ADHD* attention-deficit/hyperactivity disorder, *CAU* care as usual, *MPH* methylphenidate, *PCT* placebo-controlled titration, *SWAN* Strength and Weakness of ADHD symptoms and Normal Behavior Rating Scale

in the average daily MPH dose in MPH users, parent- and teacher-reported ADHD symptom severity, and parent- and physician-reported satisfaction with titration method. Recommendations on the usefulness of MPH treatment and dosing generated by the algorithm were followed by the treating physician in 55.1% of the cases in the PCT.

Our finding that a smaller number of children continued MPH use after PCT compared with CAU is in line with our hypothesis that PCT has the potential to detect non-responders and placebo responders. In comparison with the MTA-study [9, 18], we found similar rates of placebo responders (8.2 vs 12.5% in the MTA-study) and children with no or insufficient response to MPH (16.3 vs 10% in the MTA-study).

In more than half of the children (55.1%), physicians followed the recommendations generated by the algorithm on the usefulness of MPH treatment and dosing. To the best of our knowledge, our study is the first to implement PCT in clinical practice. Therefore, we cannot compare our findings on adherence of physicians to the recommendations provided by the algorithm to those of other studies. The rate of children continuing MPH after PCT (75.5%) and the rate of children responding favorably to MPH (65.3%) is comparable to the 70–80% rate of children responding well to MPH identified in other studies [9, 18, 20, 23]. In the CAU, almost all children (94.1%) continued MPH use following titration. Therefore, our data support the hypothesis that with CAU, a substantial proportion of non-responders and placebo responders remain undetected, and thus a substantial proportion of the children continue MPH even if they show no evidence of beneficial effects of the MPH treatment. Assuming that a number of children continued MPH in the CAU group without any beneficial effects on the severity of ADHD symptoms, this might explain our finding that there

Table 2 The development of ADHD symptoms over time for the two titration methods (intention to treat analyses)

SWAN[a] total score	Baseline				T1				T2			
	CAU		PCT		CAU		PCT		CAU		PCT	
	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*
Parent	− 23.78 (12.36)	51	− 26.45 (11.02)	49	− 12.66 (13.67)	50	− 13.47 (14.30)	45	− 12.27 (13.05)	44	− 18 (14.63)	44
Teacher	− 23.82 (12.64)	51	− 20.80 (13.46)	49	− 9.78 (15.53)	49	− 8.54 (14.11)	46	− 6.45 (15.16)	47	− 9.79 (13.75)	42
Combined parent + teacher	− 23.80 (9.82)	51	− 23.62 (8.78)	49	− 11.76 (10.76)	48	− 11.33 (10.61)	42	− 9.48 (10.67)	43	− 14.05 (10.33)	39

Values are mean ± standard deviation
Baseline prior to randomization, *CAU* care as usual, *PCT* placebo-controlled titration, *SWAN* Strength and Weakness of ADHD symptoms and Normal Behavior Rating Scale, *T1* after 7-week randomized controlled trial, *T2* after 6-month naturalistic, open-label follow-up
[a]Data represent the total SWAN scores (range − 27 to 27)

Table 3 Satisfaction with titration methods

Satisfaction with titration[a]	T1				T2			
	CAU		PCT		CAU		PCT	
	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*
Parent	79.17 (12.03)	36	79.7 (14.57)	30	80.39 (14.77)	28	81.24 (11.78)	24
Physicians	76.79 (10.25)	28	75.90 (17.22)	32	74.11 (6.08)	12	73.64 (11.62)	11

Values are mean ± standard deviation

CAU care as usual, *PCT* placebo-controlled titration, *T1* after 7-week randomized controlled trial, *T2* after 6-month naturalistic, open-label follow-up

[a]Data represent scores on the custom-made parent and physician questionnaire (available in the electronic supplementary material) on satisfaction with titration

were no significant differences between the two groups in the severity of ADHD symptoms, despite a lower percentage of children continuing MPH in the PCT group directly after titration.

Surprisingly, the number of children who discontinued MPH in the PCT group during the 6-month follow-up increased from 24.5 to 41.7%. We speculate that this change might be a postponed effect of the PCT, causing a continued critical evaluation of the effects of MPH. During the 6-month follow-up, some of these children who discontinued MPH use changed to other pharmacological agents while others discontinued any ADHD medication. Remarkably, there was no significant change observed in ADHD symptoms between both titration groups at 6-month follow-up.

Our hypothesis that children in the PCT group would be titrated more optimally compared with CAU, with larger reductions in ADHD symptom severity and with lower doses of MPH, was not confirmed, as we found no significant difference between the two titration groups in ADHD symptom severity, or the daily dose of MPH used. This result was obtained both with and without inclusion of the children where the recommendations generated by the algorithm in the PCT were followed. We speculate that the lack of differences in ADHD symptom severity and daily dose of MPH used might be due to the more protocolized version of CAU. CAU in our study may have been more structured than in general clinical practice, due to the guidelines provided and the requirement to use standardized questionnaires completed by multiple informants to assess outcomes. This structured approach is often lacking in clinical practice [19] and protocolizing stepwise titration has been shown to improve the rate of MPH responders and reduce ADHD symptom severity [17]. Therefore, the CAU in our study may have shown better treatment outcomes compared with standard clinical practice.

Current findings should be interpreted in light of some limitations. First, this study compared PCT with CAU. The recommendations generated by the algorithm were used to support decision making on MPH treatment. However, physicians were not bound to follow the generated recommendations. The recommendations were followed in somewhat more than half of the cases with the remainder deviating from the recommendations of the algorithm. This may have contributed to the lack of statistical significance in ADHD symptoms improvement and satisfaction with titration method between the two groups. Therefore, we cannot fully evaluate the potential of application of the PCT, although our findings do provide useful information on the value of PCT in clinical practice. Second, in the current study only MPH titration was protocolized. MPH is the first-choice pharmacological treatment for children with ADHD [5, 7]. However, a significant proportion of children in the PCT who were detected as placebo responders or non-responders may respond well on other stimulants [20] or other ADHD medications [36]. Other pharmacological agents, such as amphetamines [36], might be evaluated for their usefulness using PCT if treatment with MPH has not proven effective. Third, several factors may have contributed to a lack of power to detect differences between the two titration groups. Missing data for ADHD symptoms at T2 were around 10% and for the questionnaires on satisfaction with titration method were > 10%. These missing data can be attributed to the fact that this study was embedded in clinical practice and not all participants could be motivated to complete all questionnaires, despite all efforts made (i.e., reminders by e-mail and phone calls). Additionally, most physicians only completed the list for satisfaction on titration method for one single participant, while they had more than one patient participating in the study. Furthermore, we acknowledge that in the calculation of our sample size, we did not account for the multilevel approach that was chosen to analyze our data and the sample size calculation was based on detecting a significant difference between the two titration groups, rather than being optimized to detect equivalence between them. However, as the presence of the two measurements will have a beneficial effect on the statistical power, while clustering at

the other levels would have an unfavorable effect on the statistical power, it is unlikely that there is a significant difference between the results of our initial power analysis and the power of the actual multilevel analyses conducted. Fourth, we focused on developing a PCT method that could readily be implemented in clinical practice. The results of our RCT showed no difference in satisfaction rates between parents and physicians using PCT or stepwise titration. However, our PCT required titration medication kits and software for systematic registration of symptoms and side effects that will not be readily available in clinical practice, which may preclude implementation of PCT.

5 Conclusions

The current study is the first to compare the effectiveness, feasibility, and satisfaction of a PCT method to stepwise titration in order to determine whether the advantages of PCT seen in experimental settings transfer to a clinical setting. We found that PCT can better detect children who do not profit (sufficiently) from MPH treatment, thereby reducing unnecessary exposure to MPH, while at the same time reaching comparable results in terms of ADHD symptom control and parent and physician satisfaction.

Further research in larger samples is needed to draw stronger conclusions on the potential of using PCT in daily clinical practice and should include the further optimization of ADHD medication after advice to discontinue MPH treatment. Additionally, the role of potential moderators for the use of different titration methods should be taken into account as individual factors (e.g., severity of ADHD symptoms, internalizing problems, age) have been shown to partly predict response to MPH and might therefore affect the added value of using PCT. Further research should address the contribution of non-specific effects (effects that cannot be contributed to the pharmacological agent) to the overall response to MPH, as our results show, in line with recent research, that non-specific effects are an important factor in the overall response to MPH [37]. Furthermore, to facilitate the practical use of PCT in clinical practice, it is strongly advised that these medication kits and software for systematic registration of symptoms and side effects should be more readily available.

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Declarations

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Conflict of interest Karen Vertessen has been involved in a clinical trial sponsored by Takeda. The other authors have no conflicts of interest relevant to this article to disclose.

Ethics approval The local ethics committee approved the study (METC Amsterdam UMC, 2016.594) and the study was registered prospectively in the Dutch trial register (NL8121).

Consent to participate Parents and children older than 11 years provided signed informed consent.

Availability of data and material The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability The code used to analyze the data in the current study are available from the corresponding author on reasonable request.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by MB, RS, KV and AW. Professor JT was the statistical expert for this study. The first draft of the manuscript was written by KV and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript and agree to be accountable for the work.

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Authors and Affiliations

Karen Vertessen[1,2] · Marjolein Luman[1,3] · Pierre Bet[4] · Catharina E. Bergwerff[5] · Marco Bottelier[6] · Reino Stoffelsen[3] · James M. Swanson[7] · Annemiek Wisse[8] · Jos Twisk[9] · Jaap Oosterlaan[1,10,11]

✉ Karen Vertessen
k.vertessen@vu.nl

1 Vrije Universiteit Amsterdam, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands

2 University Psychiatric Centre, Katholieke Universiteit Leuven, Leuven, Belgium

3 Levvel Specialists in Youth and Family Care, Amsterdam, The Netherlands

4 Department of Clinical Pharmacology and Pharmacy, Amsterdam UMC, VU Medical Center, Amsterdam, The Netherlands

5 Institute of Education and Child Studies, Leiden University, Leiden, The Netherlands

6 Child Study Center Accare, UMC Groningen, Groningen, The Netherlands

7 Department of Pediatrics, University of California, Irvine, USA

8 Youz, Center for Youth Mental Healthcare, Velsen-Noord, The Netherlands

9 Department of Epidemiology and Biostatistics, VU Medical Center, Amsterdam, Amsterdam, The Netherlands

10 Department of Pediatrics, Emma Children's Hospital, Amsterdam UMC location University of Amsterdam, Amsterdam, The Netherlands

11 Amsterdam Reproduction and Development Research Institute, Amsterdam, The Netherlands