Administrative information

Title

Identification 1a
Effect of stimulants on growth in children and adolescent diagnosed with ADHD: study protocol for a systematic review and meta-analysis.

Registration 2
In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO)

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Contributions 3b
AD is the guarantor. JM and MC drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. JM and MC developed the search strategy. MR provided statistical expertise. All authors read, provided feedback and approved the final manuscript.

Amendments 4
If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section.

Support

Sources 5a
No funding has been received for this study
Sponsor 5b
No funding has been received for this study

Role of sponsor 5c
No funding has been received for this study
Introduction

Rationale 6

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder, with a worldwide prevalence rate of 5%-10% in children and adolescents.\(^1\)\(^2\) According to the Diagnostic and Statical Manual of Mental Disorders (DSM-5),\(^3\) ADHD is characterized by nuclear symptoms: inattention, hyperactivity and impulsivity that must be persistent and impairing.

Impairing symptoms of ADHD persist in adulthood in up to 65% of cases.\(^4\) with a pooled prevalence of adulthood ADHD 2.5%.\(^5\) ADHD suppose an enormous burden on society in terms of healthcare costs, productivity losses of family members, adverse vocational outcomes and societal financial costs. In Europe, annual national costs were estimated between 1041 and 1529 million euros.\(^6\)

While the comorbidity between ADHD and psychiatric disorders has been extensively studied, the possible association with medical conditions has received less attention. However, in recent years, it has become clear that many conditions classically thought to be nervous system disorders actually do include alterations in other physiological systems.\(^7\) As a consequence, an increasing amount of literature on the association between neuropsychiatric disorders and medical conditions has emerged in the past years.

Stimulants medications have been used for decades in the treatment of ADHD, the efficacy and safety of these drugs have been extensively examined.\(^8\)\(^9\) However long treatment periods of ADHD\(^10\)\(^11\) and persistent concerns about the effect of stimulant treatment on growth\(^12\) necessitate a deeper understanding of how ADHD and stimulant treatment may affect growth.

ADHD may be associated with dysregulated growth.\(^13\)\(^14\) Early adolescents with ADHD may have small but significant height deficits compared with controls.\(^15\) In contrast children referred for ADHD treatment are reportedly taller at baseline than those not referred.\(^12\)\(^16\)

The Multimodal Treatment Study of Children with ADHD Cooperative Group reported that untreated children with ADHD had average height Z scores that increased over time, suggesting faster growth than population norms.\(^17\)

The effect of stimulants on growth could be related with the anorexic effects and the fact that these drugs increase the availability of synaptic dopamine, which is known to acutely inhibit growth hormone.\(^12\)\(^18\) Some studies report growth reductions related with stimulant therapy\(^16\)\(^20\) and others finding no significant growth changes.\(^21\)-\(^24\) higher dosages of stimulants might cause more growth attenuation.\(^12\)\(^19\)\(^25\)\(^26\)

Moreover, growth deficits may differ based on type,\(^12\)\(^19\)\(^25\)\(^27\)\(^28\) age of initiation,\(^29\)\(^30\) or duration\(^16\)\(^31\) of stimulant medications. Limitations in the existing literature include small sample sizes, lack of controls, referred samples limiting generalizability, and paucity of information about adult growth out-comes.\(^12\)

A review of literature was performed in 2008,\(^12\) but a meta-analysis was not possible due to the large methodological differences that exist between these studies and failure of many studies to report data suitable for computing pooled effect sizes and their SEs. We hope that the new studies from the past year could shed light on this matter.
Objectives

The aim of this systematic review and meta-analysis is to evaluate the growth and final height in children and adolescents diagnosed with ADHD following different stimulants regime and how it may vary by sex and age of initiation. Our secondary aim is to evaluate the possible influence of “drug holidays”.

Methods

For this systematic review and meta-analysis, we will use methods and definitions from previous reviews and meta-analysis and performed our meta-analysis in line with approach recommended by the PRISMA statement.

Eligibility criteria

Study Designs

All original, peer-reviewed studies independently from the design (excluding case series and case studies) will be considered.

Participants

The population of interest will include children and adolescents from ages 4 to 18 years old of both sexes with:

- A categorical diagnosis of ADHD according to the DSM III, IV or V.
- Diagnosis of ADHD recorded in medical files/register.
- We will exclude studies assessing only symptoms of ADHD, without a diagnosis.
- We will exclude studies including participants with a diagnosis of minimal brain dysfunction.

Intervention

Studies will be included regardless of the past or current treatment of the participants with psychostimulants. Of interest are interventions addressing psychostimulants treatment with:

- Amphetamine
- Dextemethylphenidate
- Dextroamphetamine
  - Lisdexanfetamine
- Methylphenidate

We will exclude studies with non-stimulants ADHD drugs:

- Atomoxetine
- Alpha 2 agonist
  - Guanfacine
  - Clonidine
Drugs comparison
Using the same method as others used we calculated the Daily Dose Equivalents (DDDeq) for ADHD obtained by the Defined daily doses from www.whcc.no/atc_ddd_index. Accessed July 2015. DDDeq calculated by dividing the dosage in milligrams by the number of milligrams defined as one daily dose. The DDD is consistent for immediate-release and long-acting methylphenidate products.

The defined daily dose (DDD) is a unit of measurement commonly used within a research setting to compare drug utilization. The DDD is a calculated average maintenance dose of a drug per day when the drug is used for its main indication and does not necessarily reflect the recommended or prescribed doses per day. DDD is independent of drug price and formulation and allows a determination of drug consumption and comparison of drug use among groups.

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<td></td>
<td>15 (1)</td>
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<td></td>
<td>30 (2)</td>
</tr>
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</table>

Comparators
Reference population height tables used by the study.

Outcomes
Primary outcome: Changes in height z-score. Z-scores are often used to assess anthropometric measures to help evaluate children’s growth and nutritional status. Z-scores have a number of advantages: first, they are calculated based on the distribution of the reference population (mean and standard deviation), and thus reflect the reference distribution; second, as standardized quantities, they are comparable across ages, sexes, and anthropometric measures; third, Z-scores can be analyzed as a continuous variable in studies.

Exclusion criteria
- n < 20
- Case series or case studies
- Studies not reporting dosages
- Median follow-up < 1 year because such short follow-up would not permit detection of relevant height changes related to stimulants use
- We will exclude studies assessing only symptoms of ADHD, without a diagnosis
- We will exclude studies including participants with a diagnosis of minimal brain dysfunction
• Studies assessing non-stimulant drugs such as Atomoxetine or alpha 2 agonist (Guanfacine and Clonidine)
• Height presented in cm or percentiles

Information sources 9
Literature search strategies will be developed using medical subject headings (MeSH) and text words related to ADHD treatment.

The literature search will be limited to Spanish and English language, we will limit to human studies, but we will not apply any limitation on date of publication.

We will search:
• PubMed
• Web of Science
• Cochrane Library
• PsyclINFO

*Search strategy developed with help of José Félix Villanueva, UNAV publication services director.

In addition, we will circulate a bibliography of the included articles to ADHD experts identified by the team.

Search strategy 10
The search strategy has been developed be MC. During a couple of sessions the librarian JV reviewed and optimized the search strategy. This is the only relation of JV with the project.

After developing the PubMed search strategy it has been adapted to the sintaxis and subjects from each database.

We will search in International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov looking for ongoing studies and trials. We will also review PROSPERO looking for reviews and meta-analysis.

After the inclusion phase we will review the bibliography of included papers looking for additional studies.

At the last stage of the review we will update the search strategy to ensure that most of the eligible studies were included in the review.
PubMed search strategy:

(adhd OR attention deficit disorder with hyperactivity OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR attention deficit hyperactivity disorder OR addh OR attention deficit disorder hyperactivity OR child attention deficit disorder)

And

(height OR growth)

And

(methylphenidate OR amphetamine OR dexamethylphenidate OR lisdexamfetamine OR dextroamphetamine OR methamphetamine)

We will try to access all the selected studies. If we do not have access to an article we will try to contact the authors or get an interlibrary loan.

Study records

Data management 11a

Results of the bibliographic search will be recorded in RefWorks shared folders. RefWorks is online software for management of bibliographic information widespread.

We will eliminate duplicates using integrated RefWorks tools to find Exact Duplicates, afterwards we will develop a manual review of the articles ordered by publication date to eliminate close duplicates.

During the extraction phase data will be recorded in spreadsheets using standardized forms with Google Forms software.

The team will develop an inclusion and exclusion checklist based on inclusion and exclusion criteria that will be used during the selection process (not during the screening). A PRISMA-style flowchart will be produced to detail the study selection process and reasons for exclusion of each full-text paper will be reported.

Selection process 11b

For identifying potentially eligible records two reviewers will independently screen all records identified by the search for potential inclusion. Using Abstrackr software, the titles and abstracts will be screened against a basic-inventory with the most important exclusion criteria. We will record the reason for excluding each article.

We will resolve disagreement through discussion and when there is no consensus we will ask AD for arbitration who will adjudicate unresolved disagreements.

Abstrackr is a free, open-source, web-based software for Semi-Automatic Citation Screening. The program comprises two components; a web-based annotation tool that allows participants in a review to collaboratively screen citations for relevance, and machine learning technologies that semi-automate this process.
For selecting studies for final inclusion we will obtain full reports for all articles selected by the screening process and two independents reviewers will then screen the full text reports and decide whether these meet the inclusion and exclusion criteria with help of the inclusion and exclusion checklist.

We will seek additional information from study authors when necessary to resolve questions about eligibility. When there is no consensus we will ask AD for arbitration who will adjudicate unresolved disagreements.

Data collection process 11c
Using standardized webforms two reviewers will extract data independently from each eligible study. To ensure consistency across reviewers, we will conduct calibration exercises before starting the review.

When necessary, means and measures of dispersion will be approximated from figures in the reports using:

- Engauge Digitizer
- WebPlotDigitizer

In the absence of complete descriptions of treatments, outcomes, effect estimates, or other important information, we will consider contacting authors for missing information.

Data items 12

Publication detail
- Year
- Language
- Country

Design:
- Type of study
- Study temporality
- Time of follow-up
- Patient enrollment
- Setting
- Financial support (Bias): We will look for conflict of interest and acknowledgments within the article itself.

Participant's details
- Number
- Mean age (SD)
- Gender distribution
- Socio economic status and ethnicity
- Reference population
- Psychiatric comorbidities
- Method for diagnosis of ADHD
- DSM version used
Medication status
- Type of medication
- Dosage (mg/kg/day)
- Frequency of treatment
- Release formulation (Extended vs immediate)
- Starting age
- Duration of treatment
- Weekend break
- Holidays break

Others:
- Covariates included in the adjusted

It is possible that individual studies may consist of multiple treatment groups, such as different doses of medication. In order to avoid the possibility of introducing bias caused by multiple statistical comparisons with one control group, we will combine the groups from multiple arm studies into a single group.

Outcomes and prioritization 13

Primary outcome
Primary outcome will be the height regarding reference population at the end of follow-up of the patient. It will be measured in z-scores or number of SD.

Outcome
- Mean basal height z-score and SD
- Number of time points assessed
- Length of follow-up from diagnosis to each of the time points
- Height z-score at each time point and SD
- Last height z-score measured when patients was adult and SD

We defined adult height as the average of all height measurements performed at age ≥ 18 years for women and at age ≥ 20 years for men, consistent with criteria used in other studies.36

As has been done in other meta-analysis if needed, the mean height z-score will be calculated as a weighted average based on subgroup values (using sample size as weights).37 Also if needed, the SD of the z-score will be calculated as a pooled standard deviation based on subgroup values assuming equal variance or estimated from median and range using methods described by Hozo et al. 38

Risk of bias in individual studies 14
Most of our studies will be non-randomized so we will focus on using appropriated tools for this purpose.

Currently, there is no consensus on rating methods and appropriateness of quality assessment in meta-analyses of observational studies. 39 We will use primarily the Newcastle-Ottawa Scale, 40 which has been recommended by the Cochrane collaboration and has been used in previous meta-analysis.41,42 With it we will assess the methodological quality of the included studies, risk of bias in the selection and comparability of cohorts, and outcome.

As done in previous meta-analysis,41 two independent reviewers will undertake quality assessment and allocate stars for adherence to the prespecified criteria. Studies that scored four stars for selection, two
stars for comparability, and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability, and two for outcome ascertainment were deemed to have a medium risk of bias. Any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains, was deemed to have a high risk of bias.

Data synthesis

15a
If studies are sufficiently homogeneous in terms of design and comparator, we will conduct meta-analyses using a random-effects model.

15b
Heterogeneity will be assessed by Cochran’s Q-test and the I² statistic. A p value less than 0.05 indicated significant heterogeneity. Thresholds for the interpretation of I² can be misleading, since the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We will estimate the results with pooled relative risks and 95% confidence intervals using a Mantel-Haenszel fixed-effect model when the heterogeneity was negligible or moderate and a DerSimonian and Laird random-effects model when heterogeneity was significant. A 2-tailed p-value 0.05 will be considered statistically significant.

If we found an elevated heterogeneity we will develop a subgroup analysis to find its origin. If there were to be a clear outlier in between the studies, it would be withdrawn from the analysis.

We will use inverse-variance weighting to calculate the difference in Z-scores and SD between studies.

15c
Sensitivity analysis
Sensitivity analysis will be performed in order to explore the source of heterogeneity as follows:

- Risk of bias (by omitting studies that are judged to be at high risk of bias)
- Omitting industry funded studies

Subgroup analysis
Subgroup analyses will be used to explore possible sources of heterogeneity. A priori analysis will be:

- Patient initiation age
- Patient sex
- Type of stimulant
- Dose of stimulant
- Duration of treatment
- Follow-up period
**Meta-regression**
We will develop a meta-regression where possible to explore heterogeneity.

**15d**
A systematic narrative synthesis will be provided with information presented in the text and tables to summarize and explain the characteristics and finding of the included studies.

**Meta-bias 16**
We will evaluate whether publication bias is present creating a funnel plot. We will also statistically check the asymmetry of the funnel plot by using Egger’s test. 46,47


