

Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment*

Draft review available for public comment from October 2010 to December 2010.

Research Review Citation: Charach A, Dashti B, Carson P, Booker L, Lim CG, Lillie E, Yeung E, Ma J, Raina P, Schachar R. Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment. Comparative Effectiveness Review No. 44. (Prepared by the McMaster University Evidence-based Practice Center under Contract No. 290-02-0020.) Rockville, MD: Agency for Healthcare Research and Quality. October 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1 Public Comments		None	
Peer Reviewer #2	General: Clarity and Usability	This report was very well done. The literature review was exhaustive in order to identify the relevant studies, the studies were carefully summarized in the Tables, and the purpose and questions were described and threaded throughout the document. The document was very well organized, focused, and lead to appropriate conclusions that would be relevant for public policy decisions. This report was clearly a considerable amount of work, and the authors should be commended for taking on this task. Clarity, organization, and logic were well-done in this document.	No response required.
Peer Reviewer #3	General Comments	My general feeling is that this is a very good review of the literature, but that it may not accomplish its intended purpose. The document is “intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers”; however, the paper is then written in a style for academics. It does not look like the authors put any thought into how best to convey information to their intended audience, but instead wrote the review like they would for a journal publication.	We consider the level of writing to be appropriate. The AHRQ will create versions of this report for different users.
Peer Reviewer #3	General: Clarity and Usability	The overall clarity of the paper is okay but not great. There are awkwardly worded sentences, and there are still a few outstanding grammatical errors in the text. For example, sentences like “The ascertainment of the prevalence of ADHD across all age categories in the population is	Grammar has been more closely edited. Sentence mentioned was clarified
Peer Reviewer #3	General: Clarity and Usability	“necessary in order to appreciate the burden that the condition poses and subsequently, to ascertain unmet need, and devise services to aid in alleviating the burden” (pg 137) are grammatically correct, but very, very bad stylistically, especially in light of the intended audience.	P148 – phrase re-written: “Determining prevalence of ADHD across all age categories in the population is necessary to understand the burden the condition poses. From this, we can then identify gaps in service and develop responses which will help patients and their families in the shorter term and allow patients to meet their potential in all areas of their lives, such as maintaining fulfilling relationships and finding success in school and workplace environments.”

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Peer Reviewer #3	General: Clarity and Usability	The main problem with the review is usability. The whole review is supposed to be written for people outside of academia to make health care decisions concerning ADHD. The paper is written little differently than an academic review paper, though, and it is even being reviewed by academics! Why not have the paper also reviewed by the kinds of people who are supposed to use it to fix clarity and usability issues?	The AHRQ will create versions of this report for different users.
Peer Reviewer #3	General: Clarity and Usability	There are some grammatical errors in the text still, but mostly the text should be edited for style, as many sentences are awkward.	Refined in subsequent iterations since submission for PR comment
Peer Reviewer #3	General: Clarity and Usability	The organization throughout the paper is a little murky, and the headings can sometimes be less than clear.	We have organized by key question, and within question, by treatment, with headings that we feel are descriptive yet concise
Peer Reviewer #4	General	In general, the review looks very thorough and methodical. The comments below will focus on correcting flaws. Page numbers will refer to "page of 255", not the number at the bottom of the page.	No response required.
Peer Reviewer #4	General Comments	Thank you for the opportunity to review this impressive summary of the literature. I found it educational, and hope that my comments will be useful in perfecting it.	No response required
Peer Reviewer #5	General: Clarity and Usability	Report is well organized and clearly presented. I would like to have seen further exploration of 'psychosocial' interventions and increase clarity regarding components of intervention and variability across age groups.	Psycho-social group in non-pharmacotherapies. ES-8 to ES-11; pp38-40; pp74-77; Table 10; p85-90
Peer Reviewer #5	General: Clarity and Usability	Quality of the Report: Superior Number of Hours Spent to Review the Report: 18 This manuscript offers an excellent analysis of the complexities of diagnosis and treatment of ADHD and the confounding impact of oppositional behaviors. Key questions are clearly stated.	No response required
Peer Reviewer #5	General: Clarity and Usability	Target population is somewhat confusing as a result of inclusion of ODD and the behaviors inherent to the clinical diagnosis while separate from the presentation in ADHD. Clinical definition of ODD must be explicitly stated. While 'merely' disruptive behaviors may be described as contributing factors they may not necessarily constitute a co-morbid condition.	Explained in methods section that DSM OR ICD definitions of disorder were used; ES-4; Table 1; p12

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Peer Reviewer #6	General	This is a well done and a thorough systematic review of the extant literature. Authors address an important and a timely topic with wide-ranging evidence. I have couple of comments specifically regarding the Barkley 2000 and Shelton 2000 studies and reporting of the PATS study, details are provided below. There are occasional typos and grammatical errors requiring a very careful final reading of the report for making the needed corrections. Following are few examples from the first section (Key Question 1), however there may be other typos or corrections in the rest of the document that should be checked and corrected.	No response required
Peer Reviewer #6	General:	Clarity and Usability: Information in the tables and text is repetitive, hence makes the report very long. Otherwise the information is presented in a clear and understandable manner.	Each of the tables summarizes a different set of reports
Peer Reviewer #7	General	Ref: Separate reference list from Peer Reviewer #7	Disposition of references supplied by Peer Reviewer #7 discussed herein 4 not found before – 1 not addressed (book chapter published 2011); other 3 (1 before time frame and 2 after update, also one re:indexing terms) included anyhow as noted 4 found and excluded earlier because they didn't meet inclusion criteria during screening. Added anyhow as per PRs direction Remaining 24 made it through to level4 as part of the 440 reviewed for this question which was not part of the complete SR methodology and to be treated otherwise per Task Order Officer direction
Peer Reviewer #8	General Comments	a. General Comments: The report has great clinical meaningfulness. The target population and the audience is cleared and explicitly defined. The key questions are appropriate and explicitly stated. However, the report does not include some of relevant modern references that affect the point prevalence frequency of adults with ADHD in the US population (Kessler reference missing), the effects of medication on growth in children with ADHD (Swanson paper missing), the impact of different types of treatment on future substance use disorder in children with ADHD (Molina reference missing), and the comparative effectiveness of atomoxetine and OROS MPH (Newcorn and Michaelson reference missing).	Kessler REFID 101714 p2 of executive summary and table14 p148 and 153 Swanson - Table6 pg. 51 {20945}; Table9 p 82 {20945,3227} ; p86(text); p85 {3228 <-this is correct-i.e. only 1 digit difference from other citation above) Molina, 8 year followup: this paper was included in the review. {584} p84; {3226}p85; Table 10, p95; Table 11 p 102ish) Newcorn and Michaelson: this trial did not meet inclusion criteria, subjects were not ≤6 years and the total treatment and followup time was <12 months. {1941}

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Peer Reviewer #8	General: Clarity and Usability	<p>f. Clarity and Usability: The report is lengthy, and in an effort to be inclusive and still structured, the repetition of the outline of three questions reminded me of just how long the report was.</p> <p>I believe that the report might be shorter and organized differently. For example, it might be possible to put more of the tables now in the text into appendices. The references, which are key, are organized by their place in the text, so they cannot be scanned as easily as they might be if alphabetized. I don't think it is necessary to put in the references excluded, as the reader (and me!) might get confused as to which are the references that were used. After all, the excluded references are far easier to scan because they are alphabetized.</p> <p>I believe that the authors have worked hard to influence practice and policy decisions. It might be easier for the reader to these them out if they could be so identified in their own section. In fact, I'd rather see the future work, now devoted to possible research projects, to be removed and replaced by two sections - one on practice and one on policy. It might be possible to leave the same lead paragraphs explaining the finding and their relevance to the future, but follow with lists on practice and policy.</p>	<p>Sections on practice and policy have been added to final discussion. ES16-20; pp182-83;</p> <p>Current CER format requirements include incorporation of tables into text section</p>
Peer Reviewer #2	Executive Summary	<p>Quality of the Report: Good.</p> <p>Number of hours spent to review the report: 6 (separated into 3 sessions given length and breadth of document)</p>	No response required.
Peer Reviewer #2	Executive Summary / Results	While the authors indicated that most studies included children with the Combined subtype, it would be worth indicating whether there were any differential effects of inattention or hyperactivity/impulsivity symptom domains.	See Remaining Issues, Executive Summary ES-16 to ES-18; pp174-177 and 179-81
Peer Reviewer #2	Executive Summary / Results	While the authors have focused on ADHD and Disruptive Behavior Disorders, they seem to have excluded children with ADHD who have internalizing symptoms and learning disorders. It would be useful for the authors to comment on this. In particular, the authors discuss classroom intervention studies on p. 106, it seems that addressing the issue of learning problems would be relevant to address in this paper.	See Remaining Issues, Executive Summary ES-16 to ES-18; pp174-177 and 179-81; Learning/academic Table 5, Table 10, pp86-88; Table 111. Table 12
Peer Reviewer #3	Executive Summary	I'd especially suggest that the executive summary be rewritten with the purpose of having a plain language description of the ADHD review, since more detail is available in the body of the review. This could greatly increase the usability of the document. Suggested changes for the executive summary include:	Have greatly augmented the executive summary with additional methods and results ES-1 to ES-18

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Peer Reviewer #3	Executive Summary	1. Use simple language and tell the intended audience what they want to know in the executive summary. "What works in treating ADHD? What can go wrong? How effective is treatment" This is the information that everyone is after, so summarize this right away, as simply as possible. Then start getting in to the issues.	The AHRQ will create versions of this report for different users.
Peer Reviewer #3	Executive Summary	2. Don't use technical language at all (e.g. do not refer to population studies in sentence two, just reference them with a footnote) Describe studies in the body of the document, give only conclusions from them in the executive summary.	The AHRQ will create versions of this report for different users.
Peer Reviewer #3	Executive Summary	3. Don't get off tangent and go over things like history as in paragraph two. It looks like the executive summary is organized exactly like the body of the text, for some reason, and so goes over everything the body of the text does, even if it may not be useful in a summary.	This is an expanded executive summary from the usual because the CER ES is used as a stand alone
Peer Reviewer #3	Executive Summary	4. Rethink the organization (e.g. The Disease Burden Associated With Attention Deficit Hyperactivity Disorder (ADHD) is not a great organizational heading). The big CONCLUSIONS heading in the executive summary may also be unnecessarily confusing.	These two headings changed per Editor direction
Peer Reviewer #3	Executive Summary	5. Rewrite your key questions 1 and 2. E.g. How effective are ADHD treatments for kids under 6 years old, and what issues are there with these treatments?	These questions have been derived through AHRQ procedure and cannot be changed
Peer Reviewer #4	Executive Summary	In the executive summary, p13 of 255 (bottom p. 2), there is an erroneous statement that disruptive behavior disorders include ADHD. This was correct for DSMIII-R, but since DSM-IV in 1994, ADHD has been a separate category from disruptive behavior disorders (ODD and CD).	Re-written ES-1 to ES-18
Peer Reviewer #4	Executive Summary	On the same page, there is an erroneous statement that there were no treatments until the 1950s, when methylphenidate was developed to target the condition. This was predated by almost 20 years by Bradley's publication in the 30s of good results with amphetamine, which was used by child psychiatrists and pediatricians prior to methylphenidate. The misstatement also implies that methylphenidate was especially developed for ADHD, whereas it was actually marketed for other purposes prior to being used for ADHD.	Rewritten ES-1 to ES-18
Peer Reviewer #4	Executive Summary	The sentence starting on the same page and running to the next page reciting the history of labels for the disorder leaves out the "Hyperkinetic Reaction" of DSM-II and the attention-deficit disorder or DSM-III.	Rewritten ES-1 to ES-18

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Peer Reviewer #4	Executive Summary	On p. 14 of 255, the statement that ADHD and ICD 10 Hyperkinetic disorder closely correspond is a bit misleading. True, they deal with the same symptom clusters, but the ICD criteria rule out anyone with comorbid anxiety or depression, which constitute over a third of those diagnosable by DSM-IV. The ICD 10 criteria also don't allow for the inattentive type. Further, those with comorbid ODD or CD are diagnosed as hyperkinetic conduct disorder (HKCD), not hyperkinetic disorder (HKD). Thus the ICD 10 diagnosis is not only numerically much more constricted (only about 1/4 of DSM-IV ADHD meet criteria for either HKD or HKCD –Santosh, Taylor, Swanson, et al.), but also qualitatively different.	Rewritten ES-2, also Table 14
Peer Reviewer #6	Executive Summary	(1) on page 13 of 255 (first page of the Executive Summary, last paragraph, 4 th line from the bottom of the page), it should read: “as reflected by its being included into widely accepted classification systems” instead of “as reflected by its being included into widely accepted a classification systems.”	rewritten ES-1 to ES-2, p15, p100,
Peer Reviewer #7	Executive Summary	p. 2 co-occurring; (Ritalin) was developed...	Text changed 10 January 2011 ES-1
Peer Reviewer #7	Executive Summary	p. 3 line (L)-7 Why not United States since the rates are considerably higher there than in Canada?	US data included ES-2
Peer Reviewer #7	Executive Summary	p. 3 L-20 Why use DISEASE burden and not simply burden or family burden? The writing suggests a strong medical orientation, yet the controversial aspects of the growth of this condition suggest the need for a wider framework from which to assess the cultural, socioeconomic, educational, and sociological (e.g. family stability) aspects of ADHD.	Word 'disease' removed ES-2
Peer Reviewer #7	Executive Summary	p 4 Why is the list missing MAS and dextro-amphetamine? Atomoxetine is misspelled	List edited as per comment – 10 th January 2011 ES-4, p14
Peer Reviewer #7	Executive Summary	p. 5 L-30 “resources”	Corrected in later version ES-4
Peer Reviewer #7	Executive Summary	Of the 54% of children entering the rx phase of the PATS, what % completed and of these what % had successful outcomes? Then, from the initial cohort, what % had a successful drug outcome? The reason to raise this issue is that community use may be far in excess of these modest expectations even when given under the 'ideal' dose titration conditions of the study.	Sentences added to document that 60% entered open label titration and 46 % entered open label extension phase. Successful completion numbers not available. P46

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Peer Reviewer #7	Executive Summary	p.6 L-42 replace , with a period	Changed ES-5
Peer Reviewer #7	Executive Summary	p. 7 L-6 ...or in part...	Changed prior to PR comments ES-8
Peer Reviewer #7	Executive Summary	...report 'few adverse events' was jarring and oversimplified but the statement following it brought more balance!	No response required
Peer Reviewer #7	Executive Summary	p. 8 guanfacine is a generic name and should not be capitalized. Statement on tolerance and improved by concurrent administration of a psycho-stimulant is not a statement worthy of inclusion in an Executive Summary, in my opinion. Why assume guanfacine should be continued rather than switched to a more effective, better established drug, namely, a stimulant? Endorsing off-label concomitant use in a general summary may not be wise as there is so little knowledge of safety of combinations either short- or long-term.	"guanfacine" corrected as necessary on ES-10 and p52 as per comment 10 th Jan 2010 Conclusion about Guanfacine clarified Table2, p14
Peer Reviewer #7	Executive Summary	p. 8 L-22 The statement on long periods of time is not shown in most community treatment empirical analyses of claims data. Perhaps, the term "relatively" and from follow up studies. But even so, MTA late data are not too supportive of long-term benefits.	ES-10 10 added "relatively"
Peer Reviewer #7	Executive Summary	p8 L-33 ...in combination with...	Now 10; Changed to 'and' as per other reviewer
Peer Reviewer #7	Executive Summary	p8 L-32 this paragraph and remainder of the exec summary have no references—they would be helpful as many readers do not get to read beyond the summary.	Citations with footnotes added to executive summary ES-1 to ES-16

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Peer Reviewer #7	Executive Summary	p9 L-49-50 There is only one study (Zuvekas, 2006) that asserts that stimulant use (or ADHD tx) has leveled off and this is based on MEPS reports, i.e. parent report. The study analysis has a rather weak methodology (no confidence intervals are reported and the selection of points to measure the change may be viewed as measurement bias). The findings are not consistent with administrative claims data in the last 10 years which show ongoing growth, albeit the rate of increase may not be as steep. References: In HMO data from the west coast, Habel et al. 2005 showed a modest 4% increase from 1996-2000 among 2-18 year olds. Olsson et al. 2005 showed MEPS had a steep increase from 87-97 (.9% to 3.4%--3 fold). The analysis by Zuvekas showed a slight change from 97 to 01—a five year period in comparison to the 10 year earlier steeper change. I find the analysis serves the aim of showing non-significant growth (2.7% in 97 and 2.9% in 2001) by selecting a 5 year period in parent-reported information. The study does not generalize to all usage but only to self-reported parent sources. This is an often cited and potentially misleading study because it does not limit to parent-reported information while most other sources, particularly in Medicaid, show unabated growth in use. At best, we need to understand more about population-based rates and “unmet need” to give balanced meaning to these issues. P.9 L-51 cites US but Zuvekas and Vitiello 2006 is probably intended.	ES rewritten, see also Table 16, 17, 18, 19
Peer Reviewer #7	Executive Summary	re: affluent communities – a reference would be useful	102154 Bokhari – text amended as per comment ES-12, Table 16
Peer Reviewer #7	Executive Summary	tables on p. 10 Key ques 1: ADHD symptoms: what about improved functioning?	Changed to “improved behavior and parent skills” vii and ES-13 and ES-14
Peer Reviewer #7	Executive Summary	Key Q 1: No benefits accrue after rx is stopped so why single out the tx classroom as diminished after 2 years? This suggests a bias favoring rx therapy, in my view.	Statement removed, table modified Table 2p ES-14 and Table22
Peer Reviewer #7	Executive Summary	Key Q2: ATX gets a rosy recommendation despite its being much less effective than stimulants. Guanfacine is equally overly positive for a product that has little time on the market in which to accrue widespread usage and is based largely on off-label use.	Table 2 and Table 22; p170
Peer Reviewer #7	Executive Summary	Some comment on limitations of findings from clinical trial populations and the limited assessment of outcomes (effectiveness, safety and tolerability in community-treated youth would be helpful.	Added to discussion p51, p174 Tables 1, 2 and 3

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Peer Reviewer #7	Executive Summary	Strong level for 2.b. I agree	No response required
Peer Reviewer #7	Executive Summary	2.c same point as in above –(i.e. a reference would be useful)	{100323}102154 in executive summary and in on p170
Peer Reviewer #7	Executive Summary	p 11 L-21 ...from country to country...	Section has been rewritten ES-15(Table 3) and p106
Peer Reviewer #7	Executive Summary	p 1 L-28 measurement and diagnostic classification...	P138 now 11 Jan '11
Peer Reviewer #7	Executive Summary	p 11 L-46 Here again, the warning is about consequences of non-pharmacologic intervention but does not remind about the consequences of early use (off-label) of pharmacological agents, namely long-term safety, unknown effect on developing organs, etc.	p.1- remaining issues, prg.1, Discussed in Limitations section ES-16 to ES-18 and Limitations pp174-7
Peer Reviewer #7	Executive Summary	p. 12 L-8. At last, a clear statement about need for improved functioning.	No response required
Peer Reviewer #7	Executive Summary	p. 12 Overall, more references in the Exec Summary would be very useful and publication in a major pediatrics/child psychiatry journal would guarantee needed attention among those not likely to seek out and review the whole document.	More have been added ES-1 to ES-17; paper drafted for journal submission
Peer Reviewer #2	Introduction	The Introduction included a historical context for ADHD, and a reasonable background for setting the context of the current questions.	No response required.
Peer Reviewer #3	Introduction	Change the headings to mean something to the audience (The Disease Burden Associated With Attention Deficit Hyperactivity Disorder (ADHD) is bad)	Headings have been written to describe the content of the following sections.
Peer Reviewer #3	Introduction	I'd also suggest three main sections, one on history, one on prevalence/facts/background/diagnosis, and one on treatment, instead of the current organization.	Reorganized introductory sections
Peer Reviewer #3	Introduction	It wouldn't hurt to include ADHD in some of the headings either (e.g. history of ADHD)	Added ADHD to some headings
Peer Reviewer #3	Introduction	No significant problems with the content, just reorganize the text.	Have made significant edits to text.

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Peer Reviewer #3	Introduction	Non-pharmaceutical interventions, pg. 15 – talks only about non-pharmaceutical interventions in < 6 yrs old kids. What about > 6 yrs old? If > 6 yrs old are always treated with drugs, say so.	Report identifies section on combination behavior psychosocial and medication and also a section on academic
Peer Reviewer #4	Introduction	On p. 26 of 255, the statement that psychostimulants do not have regulatory approval for children below age 6 is erroneous. This is true for methylphenidate, but amphetamine has had FDA approval below age 6 for decades. Paradoxically, probably more methylphenidate than amphetamine is used below age 6, the opposite of the approved use.	Rewritten, Adderall is approved for ≥3 year olds in USA, and ≥6 year olds in Canada p 27 of 278
Peer Reviewer #5	Introduction	The Introduction lays the groundwork nicely for comprehensive review of ADHD, history of treatment and current context. I would like to see more regarding target audience and application of the findings in treatment (in addition to the call for further research and exploration).	The AHRQ will create versions of this report for different users. Other points addressed in discussion
Peer Reviewer #5	Introduction	Need to confirm necessity of particular review of the available evidence for preschool children (under age 6).	This review met AHRQ criteria for necessary reviews
Peer Reviewer #5	Introduction	p. 24 references resolution of disagreement by consensus regarding key study element rating however, it is unclear whether multiple reviewers actually rated the quality of the study.	Expanded text with more detail
Peer Reviewer #6	Introduction	Page 28 of 255: define psycho-social and behavioral interventions and the difference between these 2	For the purpose of this review, psychosocial and behavioral were grouped as non-pharmacological. Where individual studies are described, the interventions are described
Peer Reviewer #7	Introduction	p. 1 The introduction ignores functional impairment. This is significant because a focus on symptoms with little emphasis on functional impairment may be the reason for the ever-growing rate of diagnosis and treatment of inattention and hyperactivity. Later on, the term 'impairment' is used and then on p. 15 "associated impairment" appears. Still, the concept is not set out at the start. Impaired functioning relates to social and academic developmental markers and poses important dimensions of ADHD. If ignored, ADHD diagnosis and treatment may be justified by any visit to the doctor or school behavior complaint and would easily lead to the justification for medication. The importance of this variable could be made stronger.	for defining a 'case' which also includes showing functional impairment Added to initial paragraph

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Peer Reviewer #7	Introduction	p 13 L-7 functional impairments; excellent beginning ...condition is identified clinically in the context of society and culture... but then it seems to lose that excellent (complicated) thought. For example, p 14 L-33 ...to develop a broader approach to management strategies for ADHD and behavioral disorders. Is the medical approach too narrow? Heavily invested stakeholders (not just the industry but academic medicine, journals, media etc. When will a systematic assessment open up to the broader social and cultural context referred to on p. 13 L-11— as such additional approaches are mentioned in this review although they lack the 'quick fix' promise of a pill—increasingly more than one pill!	Suggestion noted to include broader array of approaches to consider
Peer Reviewer #7	Introduction	p. 14 L-8 prescription sales data... with mandatory company reporting requirements to the Drug Enforcement Agency	P4, 11 Jan '11
Peer Reviewer #7	Introduction	many references are quite dated now –e.g. Goldman 1998; p. 15 L-31 the Visser 2007 should be cited with the newer data	P4 updated in more recent version to 2005 data 11 Jan { 105297} Trip/Visser 2009
Peer Reviewer #7	Introduction	p. 14 L-16 Pharmacological might be preferred over pharmaceutical	Modified where appropriate throughout
Peer Reviewer #7	Introduction	p. 14 L-25 The discussion of the bill might refer to US Child... again the implications of such legislation is that systems are overstepping parental authority regarding use of medication. Concluding sentence seems to suggest more education when alternative strategies for non-medicating families might be more useful.	Discussion rewritten p4 of main section
Peer Reviewer #7	Introduction	p 14 L-46 ...methods of identification including the extent of functional impairment...	P1 changed P4,
Peer Reviewer #7	Introduction	p 14 L-52 Is the term disease needed? Could be it clinical and social burden?	P5 section header; changed
Peer Reviewer #7	Introduction	p 15 L-37 relatively few adverse events—early clinical trial information is inadequate to assess risk profiles as large community populations experience medication use.	reworded
Peer Reviewer #7	Introduction	p 15 L-50 Aren't dextro-amphetamine and MAS approved for 3-5 year olds?	Modification p59 in v7 of

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Peer Reviewer #7	Introduction	p 16 Prevalence. This topic is not clearly explained. References 26-28 are quite dated and could be updated. Part of the problem is discussing dx and rx tx in the same sentence. They should receive separate sentences because community info on the dx is more limited than on the rx tx.	reworded
Peer Reviewer #7	Introduction	p 16 L-50 identical research methods	Added 'research'
Peer Reviewer #7	Introduction	The growth in rx use from 1987 to 2003 in Medicaid very young children is quite substantial and can be referenced (Zito, et al. 2007).	Reference used
Peer Reviewer #7	Introduction	Intro p 13-16. Appendix C is not a history of ADHD; it is excluded studies	Corrected
Peer Reviewer #7	Introduction	p 13 L-29 add functional impairments	Added text
Peer Reviewer #7	Introduction	Appendix A. Question for the programmer. Amphet is in the search so it is just missing from the list of stimulants?	No treatments were excluded from the search
Peer Reviewer #8	Introduction	b. Introduction: The introduction is satisfactory and clear. The questions chosen for the review are helpful. However, there is a list of interventions, that includes only three medications: methylphenidate, atomoxetine, and guanfacine. This is not accurate, as you report on the amphetamine derived medications (mixed salts of amphetamine, mixed salts of amphetamine extended release, and lisdexamphetamine). This left-out class of medications is more widely used than atomoxetine and guanfacine together.	Drug list was updated in methods section
Peer Reviewer #2	Methods	Search strategies seemed to be exhaustive, resulting in very few studies included in this review. Description of GRADE approach on page 25 would be useful. Table 1 was a useful summary for identifying inclusion criteria for each question in this paper. Qualitative and quantitative statistics seemed to be appropriately done.	No response required.
Peer Reviewer #2	Methods	The assessment methods described on p. 37 of strong, moderate, and weak are not clearly defined. On pages 192-194, additional details are provided for individual categories. A more elaborate description is needed regarding what constitutes strong, moderate, or weak findings, this needs to be objectified further, even if the judgments are made qualitatively.	Added further explanation in Methods section and directed to copy of tool in Appendix B.

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Peer Reviewer #2	Methods / Appendix	It would be useful to have in an appendix, a glossary of all of the medications that have been discussed in this study. It is very difficult to follow the initial summary of findings with respect to medication effects, then search for information on the medications in the body of the study. This appendix should identify the main classes of medication that have been used, as well as the types in each category. This would be particularly useful as medication treatment studies were a focus in this paper.	Added list of drugs examined in the methods section of report and of executive summary
Peer Reviewer #3	Methods	The charts following the questions starting on page 10 are nice, although maybe there should be examples of things like psychostimulants that are mentioned that the intended audience might recognize.	ES key question tables: table 1c- added "e.g.; "Ritalin" example 1c; 2a "i.e.: Atomoxetine", 3c added "e.g.; "Ritalin"
Peer Reviewer #3	Methods	Figure 1 seems pretty obtuse to me, what do the arrows mean, what information is trying to be conveyed? On the other hand, table 1 is very good and seems to provide much of the information of figure 1.	Analytic framework is required by AHRQ. Made a few changes to clarify
Peer Reviewer #3	Methods	Pg 22. What is the "prevalence question"? What is "systematic review methodology"? The whole Methodology for Prevalence Question section is unnecessarily obtuse.	Added more info in Methods section and Executive Summary
Peer Reviewer #3	Methods	Pg 25. More detail about the GRADE approach would have been nice. The exact details of this approach seem to be in Appendix B, but this is nowhere stated in the Methods section. More clearly tying in the material in the Appendixes with the Methods section would have been helpful in general.	Provided further explanation of our approach in methods section.
Peer Reviewer #3	Methods	Pg 26. Quantitative Synthesis – the use of clinical judgment to pool individual study results is a weakness of the review. This may have been necessary in order to conduct the review at all, but "because I said so" is not exactly a strong, scientific method of classifying studies, and this limitation should be mentioned.	Explained that we did sensitivity analysis based on different assumptions on the correlation coefficient.
Peer Reviewer #3	Methods	Overall, the method section did a good job in describing how studies were selected for review and rated.	No response required.
Peer Reviewer #5	Methods	More clarification needed regarding the inclusion of disruptive behavior disorders, treatment interventions, and medications.	Added more detail in methods section
Peer Reviewer #6	Methods	Methods used for the review are appropriate and explicitly stated.	No response required
Peer Reviewer #7	Methods	A-4 2 to 5 ____?	Unclear

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	A-7 agonistic behavior? define.	Database search term
Peer Reviewer #7	Methods	A-8 < 1 to 6? Clarify.	Studies with children 1-6 y were not limited by publication date
Peer Reviewer #7	Methods	B-2 ADHD or sx ADHD or tx'd for ADHD	Unclear
Peer Reviewer #7	Methods	level 1 eng/comparative tx/ <6 or ≥6 if f/u 12 months	Unclear
Peer Reviewer #7	Methods	level 2 study design; dx;	Unclear
Peer Reviewer #7	Methods	level 3 population for which tx outcomes are reported?	Unclear
Peer Reviewer #7	Methods	B-4 #3 outcomes can be a comparison to other dose/timing/another tx/another type of tx/PBO/ no tx/ wait list	Unclear
Peer Reviewer #7	Methods	B-6 quality assessment tool for quantitative studies a. Selection bias i. Representative of target populations ii. % agreed to participate b. Study design	Unclear
Peer Reviewer #7	Methods	p 20 L-3 analytical framework appears appropriate and covers outcomes in great detail	No response required
Peer Reviewer #7	Methods	p 21 L-4 Table 1 PICOT is a useless acronym. I would avoid it as it is not instructive or common knowledge. Should be spelled out.	Added meanings of acronym to table
Peer Reviewer #7	Methods	p 21 L-44 Correlates for Medicaid insured youth are available and is instructive re race/ethnicity and eligibility group.	No change required

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	p 22 L-16 1997-2010 for K ₂ ; K ₃ back to 1980: why so far back when so many recent studies are available and provide information on progression of trends in the prevalence of rx use and newer methods (e.g. new-user designs, multivariate analysis (logistic regressions). These could be evaluated in an instructive manner rather than just listing the differences among studies.	Discussed in Limitations section
Peer Reviewer #7	Methods	p 22 L-15-28 time frame for searches appears appropriate.	No response required
Peer Reviewer #7	Methods	p 22 L-42 rx use only is a good criterion for usage (K ₃)	No response required
Peer Reviewer #7	Methods	p 22 L-11 to p 24 L-8 searches appear appropriate	No response required
Peer Reviewer #7	Methods	p-24 L-15 ??	Unclear
Peer Reviewer #7	Methods	p 24 L-39 review appears appropriate. Can you assure that study reports are not duplicative?	Have checked duplication
Peer Reviewer #7	Methods	p 25 L-7 quality measured re risk of bias in design and conduct of study	No response required
Peer Reviewer #7	Methods	p 25 L-11-13 8 sections appear to be comprehensive criteria	No response required
Peer Reviewer #7	Methods	p 25 L-27 5 domains for assessment: #4 what outcomes –sxs or impairment as well?	No response required
Peer Reviewer #7	Methods	p 26 L-? Synthesis appears sound	No response required
Peer Reviewer #7	Methods	p 26 L-22, 23 good	No response required

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Methods	p 27 L-13 Fig 2 Flow of studies thru review. Main exclusion is for lack of comparison tx. From 35,281 first cut to 143. This is very selective criteria and yields 53 (K ₁), 99 (K ₂), and 9 in both 1 and 2. For the prevalence studies: 8481 to 7892; excluded 589 – 130 and 35 unavailable. Used 48 of 424 reports---These numbers are not clear.	All but two reports are available for the final report Flow of studies shown in Fig 2 updated
Peer Reviewer #8	Methods	c. Methods: The inclusion and exclusion criteria are clearly stated and are practical. The search strategies are explicitly stated and logical. The definitions and the diagnostic criteria for the outcome measures are appropriate. As far as I can tell, the statistical methods are used appropriately. Because of the references chosen, I find it remarkable that some major articles on large samples published after 2006 are not included. The 8 year followup of the MTA study by Molina is not included in the references, and it reports on the increased risk of children with ADHD to substance use disorder, and the lack of protection that behavioral treatment had shown for this risk at the 3 year data was not seen later in the 8 year data. The Lilly sponsored comparative effectiveness trial published by Newcorn and Michaelson had important comparative effect size data suggesting that OROS MPH was more effective than atomoxetine in a large comparative RCT in Europe which was not cited. It appeared in the American Journal of Psychiatry 165(6): 721-730. (p. 143).	Molina, 8 year followup: this paper was included in the review. {584} Newcorn and Michaelson: this trial did not meet inclusion criteria, subjects were not ≤6 years and the total treatment and followup time was <12 months. {1941} Added as detail to discussion re atomoxetine
Peer Reviewer #2	Results	Most studies included seemed to be since 1994 based on DSM-IV criteria (at least for North American studies). Would be useful to indicate which studies used DSM-IV criteria and which did not, and whether this impacts the conclusions. Also, whether criteria for Hyperkinetic Disorder (ICD-10) was used, and whether this may impact the findings.	Rewritten for clarity.
Peer Reviewer #3	Results	Recent papers from Todd Elder and Evans, Morrill & Parente would have fit well in the Key Question 3 section. (They found higher incidences of ADHD diagnosis for the youngest kids within a given grade level).	Papers are in final report on p113 (2 paragraphs before Table13) {130016} Elder and {130011} Evans
Peer Reviewer #3	Results	This section is a very useful resource for academics and anyone else who wants more information on treatment outcomes and prevalence rates.	No response required.
Peer Reviewer #4	Results	Many of the summaries of studies talk about significant improvement in “at least one domain” without noting how many domains were tested or considering the need to correct for multiple tests.	Rewritten p43

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	On p. 61 of 255, I do not understand the handling of the Heriot et al study and do not see how one can conclude from it efficacy for both MPH and parent training. The randomized conditions are unclear, 26 children divided into 4 groups would be hilariously underpowered, and how can 12 children be 61% of 26?	Rewritten and corrected p43
Peer Reviewer #4	Results	On the same page, the description of the PATS requires clarification of the term “enrolled”. Technically, at least from the IRB perspective, anyone who signs a consent form is enrolled, but only those who pass the screen start treatment and are randomized. Usually treatment starts with randomization, so the distinction can be made by saying how many were randomized. In this case, randomization occurred after PT, so it is difficult to find the right term for those who qualified for the study and started treatment with parent training. I think you mean that 303 started PT and only 165 of those were eventually randomized to the drug conditions, but that is not clear from the way it is worded. Or did you really mean 303 consented?	Rewritten as noted ES-8 and p43
Peer Reviewer #4	Results	At the top of p.62 of 255, description of subject flow in the PATS, how did physiotherapy get into this? In the 4 th line, it is not clear what “of these” refers to. Grammatically, it refers to the immediately preceding 19 with significant improvement, but that is logically impossible.	Rewritten so that PT is spelled out as Parent Training
Peer Reviewer #4	Results	From the figures in this paragraph, it becomes obvious that the statement on the preceding page that 165 “entered ...the preliminary open label medication safety lead-in phase” was incorrect; it was actually 183, with 165 surviving. You could just drop the “and” phrase from the end of that sentence.	Rewritten as per direction p44
Peer Reviewer #4	Results	In the 3 rd paragraph on p. 62, the word “those” appears to be missing from the sentence beginning “In addition>”	Addressed in draft subsequent to that sent to PR
Peer Reviewer #4	Results	Another possible explanation for the difference between clinician and parent ratings in the parallel study phase could be that parents were comparing to the recently improved state during the titration while clinicians were comparing back to the baseline prior to medication.	NR both measures used compared to same baseline
Peer Reviewer #4	Results	In the sentence describing growth slowing, the placement of the amount may be misleading. As currently worded, it suggests that the growth expected was 1.4 cm/yr, which cannot be correct. Undoubtedly you mean that the 22 percent reduction in ht growth was 1.4 cm/yr. The 1.4 cm/yr should be moved to immediately after the 22 percent.	Rewritten p45

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	In the bolded final PATS paragraph, it is not clear whether the 18 whose parents were satisfied were included in the 19 that showed significant improvement or whether this is an additional 19. The paragraph should consider the possibility that the 34 who decided they did not want medication were also satisfied enough with the improvement that they no longer felt a need for medication.	clarified language and corrected formatting p46
Peer Reviewer #4	Results	The effect size for PATS is reminiscent of that obtained for older children with autism spectrum disorders, both less than usually reported for older typically developing children. Would you want to point that out? Either immaturity or developmental disorder seems to detract from effect size. In a similar vein, the RUPP Autism Network study found an 18% rate of intolerable side effects (requiring discontinuation) for MPH, compared to <4% for the typically developing 7-9 year-old children in the MTA. It appears that the typically developing preschoolers had a rate of intolerable side effects between those –possibly also worth noting. (It appears to be about 12-13%, but the percent should be clarified.) Here is the relevant reference: Research Units on Pediatric Psychopharmacology (RUPP) Autism Network (incl. L.E.Arnold): A randomized controlled crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry, 2005;62:1266-1274.	{101912} this article was screened out because the subjects did not have ADHD Editorial decision No response required
Peer Reviewer #4	Results	On p. 71 of 255, line one does not compute. Shouldn't the number in children and the number in adults add to either 18 or 16?	Rewritten p51
Peer Reviewer #4	Results	On p. 72, when you say more boys than girls experienced a positive response with DEX, do you mean a higher proportion or just absolute numbers? Please clarify. Also, you should give relative risk rather than or in addition to odds ratio; it's more meaningful to most readers; in fact some readers may mistakenly believe that the odds ratio is relative risk. E.g., the odds ratio of 3.4 does not mean that boys are 3.4 times as likely to have a positive response (relative risk of positive response). Readers will want to know how much more likely boys are to have positive response. This same comment applies to anywhere that odds ratio is quoted.	Publication reported as OR
Peer Reviewer #4	Results	On p. 73, top paragraph, you say that the 91 children did not have tics at baseline, but 4 lines later say that 33% of those with preexisting tics deteriorated, What preexisting tics do you refer to if none had tics at baseline?	Clarified w/o a diagnosable tic disorder p53

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	In the next paragraph on OROS MPH, you say that 63% completed the trial and 47% discontinued. That adds up to 110%. It is also not clear how 8 AEs constituted 15% discontinuing for AEs.	Rewritten p52
Peer Reviewer #4	Results	On p. 76, the description of guanfacine side effects and dropouts from the Biederman study needs some clarification. 82% is a very high dropout rate and if only a fourth of those were for AEs, what were the others for? Lack of efficacy? Were the 30% somnolence, 14% fatigue, and 13% sedation in the same patients or did a total of 57% have one of these similar side effects (mutually exclusive)? If partial overlap, how much overlap? As presented, the decrease of these 3 related side effects could be due to attrition. Did the report say whether they actually decreased in those who were still present at month 8? Or was it just an artifact of those having these side effects dropping out?	rewritten p 86 of 278
Peer Reviewer #4	Results	Ditto for the Sallee study summary.	rewritten p 88 of 278
Peer Reviewer #4	Results	The final summary paragraph for GXR may be overly optimistic given the high dropout rate in both studies. I think you should at least mention that efficacy and tolerability of GXR monotherapy was not as good as stimulants (and possibly atomoxetine?), even though it passed FDA muster as safe and effective.	rewritten p 88 of 278
Peer Reviewer #4	Results	In Table 7 you might want to asterisk pemoline as withdrawn from the market for safety considerations.	Done throughout review Table 7, Table 8
Peer Reviewer #4	Results	In Table 7, it would be logical to group clonidine trials with guanfacine as alpha-2 agonists, just as you group amphetamine and methylphenidate together as stimulants.	Have moved the one Clonidine study to directly after the Guanfacine studies ES-8, p56, Table 16
Peer Reviewer #4	Results	A lack in Table 7 is the MTA 14-month and 24-month results. Although the MTA did not use a placebo after the first month, it did have randomized treatment for 14 months showing a significant advantage of systematic methylphenidate management over intensive multicomponent behavioral treatment and routine community care. At 10-month follow-up after the end of study treatment, the advantage of the systematic medication management was still significant by ITT analysis, although at half the effect size found at 14 months, and the continued significant advantage was attributable to continuation of the assigned medication. Here are the two relevant references:	These studies are now separate Table 4 - for long term extensions.
Peer Reviewer #4	Results	The MTA Cooperative Group. A 14-Month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Archives of General Psychiatry , 56:1073-1086, Dec. 1999.	{12105} is an included article MTA discussed in another section

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	The MTA Cooperative Group. The NIMH MTA Follow-up: 24-month Outcomes of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder (ADHD). <i>Pediatrics</i> 2004, 113(4):754-761.	{8256} is an included article MTA discussed in another section
Peer Reviewer #4	Results	On p. 82, the summary of CVAs might benefit from a definition of how TIAs were determined, given the symptomatic overlap between TIAs and ADHD inattentive symptoms. Also, the sample size should be mentioned, the denominator for the 44 CVAs and 21 TIAs. Ditto for Table 8 entry.	Definition added p64, Table 8, p171
Peer Reviewer #4	Results	The increased rate of emergency dept. visits should be further explained given the documented higher rate of accidents in ADHD. Were these explained by accidents rather than cardiac or neurological events?	Definition is as described p64, p171
Peer Reviewer #4	Results	It is not clear how the order of publications in the table and order in the text were coordinated. Alphabetization does not explain the discrepancy. E.g., for GXR, Sallee comes before Biederman in the table, reverse of the order in the text.	Arranged order in tables to alphabetical (some under drug subgroups) e.e.: Table 7
Peer Reviewer #4	Results	The summary of effects on growth should point out a basic flaw in most of the studies, which involve the use of population z scores, which are cross-sectional averages at each age and do not account for the uneven pacing of longitudinal growth among individuals: each individual goes through growth phases of decreasing and increasing velocity, and those peaks and valleys occur at different times for different children/adolescents.	Editorial decision too much detail, no change required
Peer Reviewer #4	Results	On p. 94, there may be a misidentification of the 2-site, 2-yr. study that Abikoff and Hechtman carried out at NY and Montreal. I didn't print out the ref. list, but if this is the study I think it is, I am surprised to see it identified as Klein's study rather than the two PIs, Abikoff and Hechtman.	This must have been modified in subsequent version since I see nothing so ID'd in either PR OR final version.....
Peer Reviewer #4	Results	On p. 94 bottom, the age of the children in the So study would be of interest given the rather low doses of MPH.	Added p74
Peer Reviewer #4	Results	In Table 10, the results for Arnold 2003 lack a period between SES and Ethnic. Without the period it is confusing. The results of Conners 2001 is incomplete and inaccurate. The real results were Comb> MedMgt, Beh, CC; MedMgt>CC	Corrected both Table 10
Peer Reviewer #4	Results	On pp. 97-98 of 255, I am confused by the two Jensen references. The results and outcome measures look like the same study, which I believe was 2001.	Rewritten: Table 10
Peer Reviewer #4	Results	On p. 98, is not clear why Molina 2009 has different designation of intervention than the other MTA articles. Should be consistent.	Rewritten: Table 10

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	On p. 99, MTA Group 1999-120 results aren't clear. The phrase "sig increased" should be deleted or replaced by "sig improved". Also add "Beh vs. CC n.s." A summary formula might be "Comb-MedMgt>Beh~CC."	Rewritten: Table 10
Peer Reviewer #4	Results	Same page for MTA Group , 2004 -122, the first line of results should be Comb & MecMgt >Beh & CC. the last 2 lines should be Comb vs. MedMgt n.s.; Beh vs. CC n.s.	Rewritten: Table 10
Peer Reviewer #4	Results	On p. 102, there is a technically accurate statement about line 19-20 that is misleading because of the placement of "only" implying that ADHD + anxiety is helped by Beh only during the first 14 mo. there are no data to support that; it was not tested. Rephrase to make the intended meaning clear: children with ADHD who have anxiety as their only comorbidity benefit equally from MedMgt or Beh for 14 months.	Rewritten p75
Peer Reviewer #4	Results	At line 24 on the same page, it is not correct that the reduced risk for early substance use from Beh disappears by 22 mo. after cessation of Tx. A different analysis using a different definition of substance use (adjusted for developmental age) does find a protective effect of Beh at 36 mo. (22 mo. post-treatment). I believe it's reported in Molina 2009, certainly presented at symposia.	Molina study is included{584} Presented at symposia. It is not in the 2009 paper. This statement is as in publication. Did include fact that different analysis has been presented
Peer Reviewer #4	Results	At the bottom of p. 102, it's hard to believe there was only one report of a behavioral Tx for parents of children with ADHD. What about all the parent training studies?	These are results for long term studies, not all treatment studies
Peer Reviewer #4	Results	The summary of academic outcomes (Pp.103-104) should clarify the difference between achievement (as documented on standardized tests) and academic performance (as documented in grades, homework completion, etc.).	There are a lack of details to answer this. Discussed in Limitations section P 121 of 278
Peer Reviewer #4	Results	On pp. 108—109 of 255, it should be clearly noted that these studies were not randomized and self-selection may well account for any protective effect found for stimulant treatment. In fact, a larger study that these, the MTA (Molina et al, 2009) at 8-year follow-up found no effect of stimulant treatment (either risk or protection) on substance use at ages 15-18, examined several different ways.	Molina study {584} is included P 128 of 278 rewritten
Peer Reviewer #4	Results	At the bottom of p. 109, it should be noted in the Charach study that causation cannot be concluded. It may be that adherence results in few adverse symptoms or fewer adverse symptoms results in better adherence or both are caused by SES determinants of adherence and adverse symptoms.	P 128 of 278 rewritten

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	The summary on p. 110 is overly optimistic about effects of stimulant on substance use, and relatively neglects studies that show increased risk or no association. The most reasonable conclusion from all data considered is no association.	rewritten p 128 of 278
Peer Reviewer #4	Results	In the discussion of different diagnostic criteria (p. 114-115), it would be important to mention that only ¼ of the MTA sample of combined type ADHD met the IDC-10 criteria for hyperkinetic disorder or hyperkinetic conduct disorder. The relevant reference is:	Editorial decision, too detailed for section
Peer Reviewer #4	Results	Santosh PJ, Taylor E, Swanson J, Wigal T, Chuang S, Davies M, Greenhill L, Newcorn J, Arnold LE, Jensen P, Vitiello B, Elliott G, Hinshaw SP, Hechtman L, Abikoff H, Pelham WE, Wells K, Posner M. Reanalysis of the Multimodal Treatment Study of Attention-Deficit/Hyperactivity disorder (ADHD) based on ICD-10 Criteria for hyperkinetic disorder (HD). Clinical Neuroscience Research, 5(5-6):, 2005.	{22301} excluded at level 1, it did not include subjects ≤6 years of age or long-term outcomes. P116/320 added as per PR suggestion
Peer Reviewer #4	Results	On p. 116, the discussion of teacher ratings should make the distinction between teachers in regular classrooms who have many normal children to compare to and teachers in special small classes with only other aberrant children to compare to and good class structure that suppresses symptoms. The excellent behavioral programs in some small well-staffed classes	No reference for this statement Inclusion criteria required comparison of two groups with defined disorder ES-7, ES-13, p38, p166, p168
Peer Reviewer #4	Results	In Table 13, p. 119, I believe DSM-II used the term “hyperkinetic reaction of childhood,” not syndrome. Rutter’s Isle of Wight study occurred before the term ADHD was invented, so could not technically ascertain prevalence of ADHD, only MBD or other related concept.	Changed as per recommendation in all instances p139 17 12 2011
Peer Reviewer #4	Results	On p. 121, the DSM-III released in 1980 used the term attention-deficit disorder, with a modifier with or without hyperactivity. ADHD came only later with DSM-III-R.	rewritten p 132 of 278
Peer Reviewer #5	Results	Studies are clearly described, key messages explicit and applicable and figures, tables and appendices adequate.	No response required

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	<p>Key question 1</p> <p>Table 3, page 44 and 47 of 255</p> <p>Study results for Nixon 2001 and Weeks 1997: No results are reported under parent competence. If parental competence was not measured in the study, it should be so stated.</p> <p>Study results for Schuhmann 1998 and Hood 2003 studies: Under Parent competence, it is reported that maternal perception of child behavior more positive than paternal perception. It is unclear how this difference in maternal and paternal perception related to whether the PCIT sessions were attended by mother, father or both.</p>	Table 3 pp26 to 30 rewritten
Peer Reviewer #6	Results	<p>Table 4, page 54 of 255</p> <p>Study results for Shelton 2000: Under Parent competence, it is reported that there were no benefits in parenting program post 1y. However, it is important to emphasize very significant study limitations regarding the parenting arm of the study. For example, neither the children's caregivers nor their teachers had indicated impaired functioning in the kindergartners included in the study. There is evidence that psychosocial treatment approaches have greater impact on those children rated with higher levels of problems (Kellam et al. 1998; Wilson and Lipsey 2007). Furthermore, only 25% of the parents attended more than four parent behavior training sessions.</p>	<p>Reports must meet inclusion/exclusion criteria to be included: the population in Kellam does not have ADHD and the Wilson and Lipsey paper is a meta-analysis (not included) Done by AC?</p> <p>Table4 -modified as per suggestion of Peer Reviewer</p>
Peer Reviewer #6	Results	Table 5, page 60 of 255, McGoey 2005 study results, under Intervention duration, need to spell out what does IYSS stand for in the Abbreviation legend for the table.	Removed reference to IYSS
Peer Reviewer #6	Results	Table 6: general comments about reporting of the PATS study results in Table 6. There are 5 different reports cited in Table 6 that are related to the PATS study. To avoid confusion it should be clearly indicated in the table that the results reported from these 5 PATS studies pertain to one study and do not represent 5 different samples.	Added 'PATS' to cells Table 6
Peer Reviewer #6	Results	Table 6, page 66 of 255, Ghuman 2007 study: Author's first name initial is incorrect; the author name should be changed from "Ghuman R" to "Ghuman J."	Corrected in table Table 6

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	Table 6, page 67 of 255, results for the Ghuman 2009 study, under Sample N, Mean age, and % Male: it is incorrectly stated that % of males in the study was not reported. This information is provided on 2 nd line on page 331 of the “Ghuman JK, Aman MG, Lecavalier L, Riddle MA, Gelenberg A, Wright R, Rice S, Ghuman HS, Fort C. Randomized, placebo-controlled, crossover study of methylphenidate for attention-deficit/hyperactivity disorder symptoms in preschoolers with developmental disorders. J Child Adolesc Psychopharmacol 2009 Aug; 19(4):329-39” article, and reads: “There were 13 boys (92.9%) and 1 girl.”	Added data to table Table 6
Peer Reviewer #6	Results	Table 6, page 68 of 255, it should be indicated that the Musten 1997 and Firestone 1998 study results are from the same sample of children. The Firestone 1998 study results need to show which interventions were compared.	Added text to table Table 6
Peer Reviewer #6	Results	Table 6, page 68 and 69 of 255, for the Heriot 2007 and Barkley 1988 studies, no information is provided under the results for safety, if safety information is not provided in the articles, it should be so stated.	Added data to the table Table 6
Peer Reviewer #6	Results	Page 67 of 255, last sentence in the section labeled Summary and Limitations misrepresents study findings reported in the Ghuman 2007 PATS study. The Ghuman 2007 PATS study does not report a decrease in MPH effectiveness in those children who have more psychosocial adversity, and proposes no causal relationship between MPH effectiveness and psychosocial adversity. Rather it reports that the children in the High comorbidity subgroup were found to have more family adversity, which is an association that was found and not a causative relationship. It is clearly stated in the 2 nd paragraph on page 576 of the “Ghuman JK, Riddle MA, Vitiello B, Greenhill LL, Chuang SZ, Wigal SB, Kollins SH, Abikoff HB, McCracken JT, Kastelic E, Scharko AM, McGough JJ, Murray DW, Evans L, Swanson JM, Wigal T, Posner K, Cunningham C, Davies M, Skrobala AM. Comorbidity moderates response to methylphenidate in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS). J Child Adolesc Psychopharmacol. 2007 Oct; 17(5):563-80” study, that “family adversity did not have a main effect on MPH dose response”. However, the “children in the High comorbidity subgroup were found to have more family adversity.”	rewritten 69 of 278; now p44 and Table 6
Peer Reviewer #6	Results	Key question 2 Pemoline is not discussed in the text, but studies on pemoline are included in Table 7.	Weak studies are not included in text

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	Page 92 of 255, under description of the MTA study: Were AEs different in the combined treatment group since the combined treatment group ended maintenance on a lower dose than the medication only group?	p.94 AEs not directly addressed in the studies published of combined Tx.
Peer Reviewer #6	Results	Key question 3 Page 115 of 255, 2nd paragraph: What does ICF stand for?	Added explanation before ICF
Peer Reviewer #6	Results	Page 138 of 255, under Key Considerations, Overall, last bullet point states that appreciation of the combined neuro-developmental and environmental etiologies and magnitude of impairment due to the condition has increased over the past 4 decades. However, there was no discussion of this conclusion in the preceding text.	Bullet point removed in rewrite
Peer Reviewer #6	Results	(2) on page 45 of 255, Table 3, Dadds 1992 study, under Interventions completed and Results for Child behavior, what does <i>ally</i> mean? It seems like a typo, if it is not, it needs to be explained what it stands for.	Added explanation in table cell
Peer Reviewer #6	Results	(3) on page 62 of 255, first line: while describing the PATS study, it states “279 entered <i>physiotherapy</i> ” – need to correct this obvious error. Same page, 3 rd paragraph, 8 th and 9 th lines: should “In addition, noted to have more comorbid conditions” read “In addition, <i>those</i> noted to have more comorbid conditions?”	Both changed in draft subsequent to one received by PR
Peer Reviewer #6	Results	(4) on page 63 of 255, first paragraph, first sentence: need to change “adverse events” to “Adverse events” at the beginning of the sentence. Same page, 3 rd paragraph, 4 th line: need to change “ <i>theparallel</i> phase” to “ <i>the parallel</i> phase.” Same page, 4 th paragraph, 2 nd line: “ <i>whil</i> on MPH” should read “ <i>while</i> on MPH.”	All noted and changed in final draft
Peer Reviewer #6	Results	(5) Table 6, page 66 of 255, Ghuman 2007 study: Author’s first name initial is incorrect; the author name should be changed from “Ghuman R” to “Ghuman J.”	Corrected in table Table 6
Peer Reviewer #6	Results	(6) on page 74 of 255, first paragraph under Atomoxetine, line 15, “There were no <i>clinical</i> meaningful differences in laboratory values” should be changed to “There were no <i>clinically</i> meaningful differences in laboratory values.”	Corrected in text Table 6
Peer Reviewer #6	Results	(7) on page 107 of 255, Table 11, Molina 2009 study under the Results section: “Tx not differ” should be changed to “Tx <i>did</i> not differ.”	Changed in table Table 6

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 29 L-12 Spell out PCIT occasionally so readers can learn this acronym.	AHRQ guidelines require the spelling out of an acronym once per chapter
Peer Reviewer #7	Results	p 29 L-33 spell out IYPP	Spelled out earlier
Peer Reviewer #7	Results	p 30 L-20 mention the quality criteria here re weak, moderate and strong assessments.	Added some text to explanation
Peer Reviewer #7	Results	p 38 L-14 A statistical review might be useful on the assumption that correlation coefficient between post and pre tx scores is 0.5.	p.33, prg.1, sensitivity analysis was done and reference to it included
Peer Reviewer #7	Results	p 40-41 Fig 5 and 6 Forrest plot organization is reverse of that of Fig 3 and 4—why? Tables and figures titles should spell out the outcomes so readers can readily understand the tables. Unknown jargon is not helpful.	Statistician does not recommend changing because it will interfere with interpretation. Abbreviations used updated and corrected
Peer Reviewer #7	Results	p 42 Re long-term extensions of CTs of parenting interventions: a major concern I have is the inference stated that there is efficacy for preschoolers but ignores the important difference in preschool vs. older youth findings. Alternative could be: L-16 ...3-6 years ^{41,52} . However, high attrition suggests preschool responders are a smaller pool of CT subjects than in studies of ≥6 year olds. I don't see how it is correct to say "limiting interpretation of the results"—maybe it limits generalizability but in terms of the primary outcome it suggests a weakened, selective benefit. As stated, the inferences appear the same as for older youth which is an overstatement, in my opinion.	Changed text about limiting interpretation
Peer Reviewer #7	Results	p 44 Table 4 what is the meaning of +ve? P. 43-45 Column 3 heading is unclear –attrition rate is 100% but what do prior numbers refer to (84:4y8m 100%). There may be a legend somewhere, but I could not find it.	Text in table clarified Table 4
Peer Reviewer #7	Results	p 46 L 3 and 4 Combinations of parent training and school/daycare interventions for DBD or ADHD in preschoolers. Is it possible to show the lower participation rates of low SES parents in MCI?	refID 613 (now added)
Peer Reviewer #7	Results	p 48 Table 5 study design quality rating differs from earlier tables.	Corrected Table 5
Peer Reviewer #7	Results	p 50 reference 85 is no on table or described in the text.	Matched text with tables for completeness

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 50 What are the funding sources for the studies? It would be useful on the tables for the rx studies, in particular.	Have not added this to tables
Peer Reviewer #7	Results	p 50 L-23 Biased, non-credible statement since MPH ADEs have been so well established. Authors may report such short term experience but what is the reason to endorse it here?	It is standard to report outcomes in placebo and compare with intervention group
Peer Reviewer #7	Results	p 50 L-29 contradicts/contrasts with L-23 on ADEs.	No response
Peer Reviewer #7	Results	p 54 pharmaceutical is used here but psychopharmacologic is a more common choice.	Changed in post Peer reviewer version
Peer Reviewer #7	Results	p 59 Limitations of PATS do not show the smaller responder pool compared with older youth.	Comparison with older children not a focus
Peer Reviewer #7	Results	K ₂ Long-term outcomes in youth	Questions are set by AHRQ process, and not changed
Peer Reviewer #7	Results	p 60 L-21 atomoxetine (lc); guanfacine (lc). Generic names are not capitalized.	pp 5, 8, 57, corrected as per prior comment by pr
Peer Reviewer #7	Results	p 60 L-31 Industry is mentioned in the text but would be good on the tables—funding source so that reader can assess the impact on results.	Data has not been added to tables; further discussion in text
Peer Reviewer #7	Results	p 61 L-17 It would be useful to note the limited generalizability.	Unclear
Peer Reviewer #7	Results	p 61 L-40 non-significant	Unclear
Peer Reviewer #7	Results	p 67 Table 7. Spell: atomoxetine	Corrected in document
Peer Reviewer #7	Results	p 61 Ref 98 good assessment – clear. Gives equivocal support for long-term use of stimulants.	No response required
Peer Reviewer #7	Results	p 62 L-7 significant? 95% CI 0.31, 4.40—not to my eye.	Added sentence to clarify meaning

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Peer Reviewer #7	Results	p 62 L-9 1.85)) remove one.	Fixed edited p53
Peer Reviewer #7	Results	p 62 L-20 (N=2).	Fixed typo
Peer Reviewer #7	Results	p 62 L-21 mm'l'?? MMT?	Rewritten for clarity
Peer Reviewer #7	Results	p 62 L-47 mean bp change increased by... Sentence is unclear.	P61 changed p54
Peer Reviewer #7	Results	p 63 L-24 relatively lower doses; it is not possible to infer effectiveness from the dosage.	Changed to efficacious p55
Peer Reviewer #7	Results	p 63 L-26 available on...	Modified in subsequent draft
Peer Reviewer #7	Results	p 63 L-33 for use in the...	Changed
Peer Reviewer #7	Results	p 63 L-53 Since subjects were withdrawn from previous medications, how are we to know that AEs relate to the study intervention (ATX vs PBO) and do not reflect withdrawal effects or previous irreversible adverse drug effects? Also, relapse prevention studies are known to be flawed by withdrawal difficulties.	Information about withdrawal effects for ATX not addressed in papers
Peer Reviewer #7	Results	p 64 L-37 replace 'long periods of time' with 12 months.	Changed text
Peer Reviewer #7	Results	p 64 L-43 very strong endorsement of atomoxetine with no information on funding sources. Its use is falling and often it is combined with a stimulant suggesting it is not effective by itself.	Discussion of ATX changed; Table 2 and 22
Peer Reviewer #7	Results	p 64 L-49 Open label extensions are fraught with limitations due to 1) continuation of tx responders; 2) lack of blinding. Addition of GXR to psycho-stimulant is also confusing. Credibility is questionable, although AEs and high withdrawal rates would make the efficacy findings for GXR moot. These findings leave the impression that FDA approval voters ignored the data!	Discussion of GXR changed to reflect points Table 2 and 22

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 66 L-7 Summary is certainly optimistic and confusing. Not only is tolerability improved with concomitant stimulant use but effectiveness due to the stimulant can't be ruled out either. I suggest a more circumspect summary.	Rewritten p165
Peer Reviewer #7	Results	p 71 ADEs; p 74 L-14 ref 105 says atomoxetine but med column say MPH; MASXR.	Corrected in table Table 8
Peer Reviewer #7	Results	p 74 L-37-50 Is this industry funded observational study which may lack power to show differences?	Report descriptive open label extensions, not all with comparison groups for the extensions
Peer Reviewer #7	Results	p 75 L-36 How are vascular events interpreted? Is comparison to no treatment a fair comparison? Should be defined better.	Page reflects data in studies
Peer Reviewer #7	Results	p 78 L-7-27 Summary: this conclusion does not appear to acknowledge the 25 yr+ collective body of work on growth effects related to stimulant use. Also, it appears to minimize the effects.	Section added after Table 8 addressing this issue directly
Peer Reviewer #7	Results	p 79 L-20 Should weakly designed study findings be left for readers to synthesize? Not an instructive approach.	p.80, prg.2, Liebson paper removed, readers directed elsewhere
Peer Reviewer #7	Results	p 79 L-32 Effects on height and weight are not explained.	readers directed elsewhere
Peer Reviewer #7	Results	p 80 L-29 Swanson has more valid data than a study of chart review. So again, the summary is not especially insightful.	p.81, summaries edited, Swanson info included with study description
Peer Reviewer #7	Results	p 81 L-23 A good idea to organize studies by validity. By 3 year, MTA showed no difference among interventions but all improved from baseline. Should discuss the impact of being in a research study (e.g., volunteer bias, expectancy effects and non-intervention impact of study participation).	Too detailed
Peer Reviewer #7	Results	p 82 L-25 Not sure how trajectory at 3 years predicts at 8 years given that there was no significant difference in the distal outcomes cited. Unclear.	Language changed
Peer Reviewer #7	Results	p 82 L-46 Spell: Caucasians	Corrected spelling
Peer Reviewer #7	Results	p 83 L-3 Swanson height and weight data are not persuasively repeated in the ADE section on growth p. 78.	reader directed elsewhere

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 83 L-23 Naïve statement: that combination therapy would attenuate sx's when drug withdrawal may not be precisely understood.	too detailed
Peer Reviewer #7	Results	p 91 L-12 effect size ___??	See Tables 1 and 2, and information repeated in Table 21 and 22
Peer Reviewer #7	Results	p 91 L-30 Comparing Asian to US dosing ignores biological differences in drug metabolism based on race as the rationale for lower doses in the Chinese.	added comments about genetic and cultural differences
Peer Reviewer #7	Results	p 93 L-45 Could multiple comparisons explain the findings?	p.97, rewritten, as stated in publication
Peer Reviewer #7	Results	p 94 L-39 Again, non-pharmacologic intervention response impersistence is underscored when, in fact, few long-term or ongoing outcomes of medication are found.	language adjusted
Peer Reviewer #7	Results	p 94 L-52 Emphasized again in the summary.	rewritten
Peer Reviewer #7	Results	p 97 Very long term outcomes: these studies again suggest a lot of data mining and one wonders if these are type I errors, based on multiple comparisons.	rewritten, discussed as in publications
Peer Reviewer #7	Results	p 98 L-25 bupropion	Corrected spelling
Peer Reviewer #7	Results	p 98 L-37 statistically	Corrected spelling
Peer Reviewer #7	Results	p 98 L-43 Comparison between med vs combined tx may not differ but what was the impact compared to expected rates in non-ADHD population?	Not compared
Peer Reviewer #7	Results	p 103 K ₃ Variation in diagnostic prevalence by geography, time period, provider type and sociodemographic characteristics. This section does not differentiate enough between diagnostic prevalence (clinician-reported) and true prevalence (by research criteria) and use of psychotropic medication for ADHD.	Discussion added to introduction for KQ3 under methodological considerations

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 103 L-24 by shaping detection in the larger population: huh? There are substantial differences in dx based on reimbursement claims that are difficult to assess beyond justifying the use of medication or the clinician's view of the symptoms (with no estimate of impairment). It surely must be taken cautiously as a measure of true prevalence. And of course, other factors enter into it: parent preference, insurance coverage, etc.	Discussion added to intro for KQ3 under methodological considerations
Peer Reviewer #7	Results	p 103 L-32 remove in	Sentence modified
Peer Reviewer #7	Results	p 103 L-35 of the spectrum... and those who...	Changed p100
Peer Reviewer #7	Results	p 103 L-50 burgeoned; ...highlighting...	Changed p100
Peer Reviewer #7	Results	p 103 L-51 individuals:	Changed p100
Peer Reviewer #7	Results	p 104 L-45 omit 'estimation'	Sentence modified in prior draft
Peer Reviewer #7	Results	p 105 L-13 and L-14 reference numbers are not correct	Corrected refIDs
Peer Reviewer #7	Results	Is ref 178 related to the text? Stevens in 180. Mattox and Harder (181) is not on the reference list.	Corrected refID
Peer Reviewer #7	Results	p 105 L-33 pharmacological research	P112 changed as per review
Peer Reviewer #7	Results	p 105 L-41 Is it a bill or a law? Citation uses Bill which is confusing.	Amended Table14 (p105)
Peer Reviewer #7	Results	p 105 L-35 ... by a medical professional	In table: NLM and CDC website cite "... health professional" Table 14
Peer Reviewer #7	Results	p 105 L-37 influence on ...diagnosed by...	Amended Table 14

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 105 L-39 child on medication	Amended Table 14
Peer Reviewer #7	Results	p 105 L-46 interpretation beyond... norm in... grammar; meaning is still unclear. ... classroom, highly subjective.?	Amended Table 14
Peer Reviewer #7	Results	p 105 L-56 paragraph starts with a run-on sentence. Pls edit.	Edited p112
Peer Reviewer #7	Results	p 106 L-16 Emphasis on Canadian administrative claims study (ref 26) but no US studies.	Kessler is cited elsewhere {101714} see Greenhill comments
Peer Reviewer #7	Results	p 106 L-33-36 Conclusion misses the point. Trying to relate valid/reliable diagnosis with clinically reported diagnosis and then treatment rates by geography/time period/provider/sociodemographics. (as in #86 above)	Discussion of this point added to intro sections of KQ3 under methodological considerations and comparison of underlying prevalence with clinical identification and subsequent treatment
Peer Reviewer #7	Results	p 107 L-20 Identifies response to d,l-amphetamine inpatients—or residential school youth?	Psychiatric inpatients
Peer Reviewer #7	Results	p 108 L-10 Table 13 ... for ADHD (column 4)	Added 'for' Table 13
Peer Reviewer #7	Results	p 108 L-15 with it_??	Added 'it' Table 13
Peer Reviewer #7	Results	p 108 L-36 Glad to see the Isle of Wight study mentioned (prevalence 0.9%)	No response required
Peer Reviewer #7	Results	p 110 L-7 A more recent reference is preferable.	This reference is from the time in the timeline
Peer Reviewer #7	Results	p 110 L-17 DDD reference? And L-19 unclear. Prescriptions are not persons, so why use this?	Indication of drug use

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 111 L-3 Poor choice of others; 13 is the law and 214 is an obsolete article in JAMA from AMA committee. Restricts inappropriate use to studies to verify it when the growth in stimulant use from secondary sources (claims data and federal surveys (NAMCS/NHMCS) cannot establish appropriateness. But, biased inference may be made since there is an obvious increase in community-based diagnostic rates from Froelich (2077) and Merikanga. Discussion misses some of the most prominent users (ref 5,6,7).	Tables revamped in section 3; table 15 US data now; table 16 international; JZ's suggestions from ref list added
Peer Reviewer #7	Results	p 111 L-38 Why is 2005 legislation here? Seems confusing. Is environment actually referring to other (social and economic) factors? Environment takes on a much wider meaning for some readers.	P115 changed to social and economic factors; 2005 legislation chosen to bookend with 1879 Educational Act
Peer Reviewer #7	Results	p 111 Table 14 No distinction between diagnosis and prevalence of rx use.	As per PR Comment 152 (below)
Peer Reviewer #7	Results	p 111 L-25 update reference to 2007	Done {4999} = Kessler 2007
Peer Reviewer #7	Results	p 112 L-5 add diagnostic before prevalence in the title.	Per comment 150(above) done Table 14 p123
Peer Reviewer #7	Results	p 118 5.29% ADHD <19 y/o worldwide: the % use of stimulants in US in selected subsets e.g. Medicaid, exceeds this rate.	P129 change made in SE and in body of text
Peer Reviewer #7	Results	p 118 Geographic, temporal, provider type and/or sociodemographic factors.	P129 changed p109
Peer Reviewer #7	Results	p 118 L-54-57 How does "though not all studies (ref 226)" relate to the next sentence on Puerto Rico study which shows greater gender and inverse age effects. Ref 229 and 230 are out of sync with vast literature, so why focus on them? Not all studies are of equal merit. Single studies with contrary findings raise questions about the method that merit explication and caution.	Added summary statements in introductory paragraph of this section and again in final summary that emphasize overall gender and age effects
Peer Reviewer #7	Results	P 119 L-33 ratio	P130 changed
Peer Reviewer #7	Results	p 120 L-52 percent,	Unclear to which this refers; however, AHRQ guidelines prescribe "percent" in text but % in brackets.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 120 L-19-29 Comparisons in various age group and with differing diagnostic ascertainment tools makes this text tedious and not too useful.	Para (p131) tweaked
Peer Reviewer #7	Results	L-26 European No. of Russia, huh?	Text changed Table; differentiating between European vs Asian portion of that nation
Peer Reviewer #7	Results	Mean age 13.8 does not tell the inclusion range.	Leung et al, {105873} inclusion range not reported.
Peer Reviewer #7	Results	p 120 L-32-52 Why is the text bolded?	Corrected on subsequent version
Peer Reviewer #7	Results	p 120 L-39 ; is used when a comma seems appropriate here and throughout the entire text.	Grammar edited throughout report
Peer Reviewer #7	Results	p 120 L- 46 Decreasing diagnosis from pooled prevalence in meta-regression is questionable as later suggested by the authors.	Amended p133 of current tracked version
Peer Reviewer #7	Results	p 121 L-13 and L-28 Separating clinician-reported (could also be called treated prevalence) from research-quality diagnosis is important. Mixing rx with dx information is confusing.	See Tables 15 through to 18
Peer Reviewer #7	Results	p 121 Ref 28 quite dated when 10 year trends (87-96) were published in Arch Ped and Adol Med (2003) which features analysis of stimulants within the paper.	P133 updated results to reflect PRs more recent data {102770}
Peer Reviewer #7	Results	p 121 L-22 Great emphasis on race/ethnicity from MEPS creates bias because of sample selection of volunteers, recall and measurement bias due to restriction to those who come to treatment! The most profound and detailed differences in race/ethnicity come from Medicaid claims data where denominators include all enrollees. Alternatively, when single years are combined, race/ethnic-specific prevalence of use of medication can be assessed from NAMCS and NHMCS federal surveys.	Section on treatment reorganized
Peer Reviewer #7	Results	p 122 L-19 Ref 244 is somewhat misleading: disproportionately Caucasian. Isn't the point that non-white have disproportionately lower rates of use?	P134 Amended and {102197} Zito added too. Tables 15 through to 18

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 122 L-19 ref 249 There is a confusing mix of treated prevalence data with stimulant prevalence of use in this section. Separate sections would be useful. An introduction could clarify the data sources: fed surveys e.g. NAMCS/NHMCS and MEPS discuss MEPs as a particularly narrow population discuss admin claims data sources (HMO records; Medicaid which are patient-level data) and DEA sales data from industry sources in ARCOS database which are not patient-level data	Section on treatment and stimulant reorganized. Data sources emphasized and section organized to some extent by data source. Details about strengths weaknesses of data in intro to KQ3
Peer Reviewer #7	Results	p 123 L-1 could add Zito et al. 2003	Amended p135 {102197} Zito added too.
Peer Reviewer #7	Results	p 123 L-5 what does treated prevalence refer to?	Adult ADHD as per sentence below and on p134 in newer draft
Peer Reviewer #7	Results	p 123 L-14 Validity of telephone diagnosis re symptoms alone?	Changed p140
Peer Reviewer #7	Results	Brief summary: Plateau stated in Zuvekas is not borne out by other studies (CDC showed a 12% increase in 4 years (2004 to 2007); Habel et al. modest increase; Medicaid greater increase. Emphasizing the RATE OF INCREASE is not as important as the ongoing larger pool of individuals, which may be driven by DSM emphasis on symptoms, allowing concomitant diagnoses and hence concomitant psychotropic class use—a topic of concern because of off-label use and little safety or tolerability data.	See section on Time trends where many more papers are included and point made that medication use appears to be continuing to the present time. in section under medication treatment
Peer Reviewer #7	Results	Overall, this section could be reorganized to make a more coherent presentation of information from observational research. The Brief summary in US L-18 would omit the plateau because it is based on a single, arguably flawed analysis (Zuvekas MEPS study).	See section on time trends where many more papers are included and point made that medication use appears to be continuing to the present time. in section under medication treatment
Peer Reviewer #7	Results	p 123 L-19 omit “some” it is widespread in all Medicaid data and most physician survey data.	P158 changed as per PR recommendation
Peer Reviewer #7	Results	p 123 L-24 omit some: regional variation is well established.	P158 changed as per PR recommendation
Peer Reviewer #7	Results	p 123 L-47 practitioners is misspelled	P135 (buttoned) or 159 (this final draft) changed as per PR recommendation

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Peer Reviewer #7	Results	p 123 L-55 Prevalence in what time period?	P135 (buttoned) or 159 (this final draft) changed as per PR recommendation
Peer Reviewer #7	Results	p 124 L-25 Compared to U.S.... a relatively low prevalence but higher than in other western countries, e.g. UK and Italy.	P135 (buttoned) or 159 (this final draft) changed as per PR recommendation
Peer Reviewer #7	Results	p 124 L-27 Omit 'appear to be'—this is also another well-established difference.	P135 (buttoned) or 159 (this final draft) changed as per PR recommendation
Peer Reviewer #7	Results	p 124 L-29 Important finding: ...attributed to more case finding and prescription...	P136 (buttoned) or 159 (this final draft) changed as per PR recommendation
Peer Reviewer #7	Results	p 124 L-32 Omit period, time trend is common usage. Why is this paragraph in bold type?	P136 (buttoned) or 159 (this final draft) changed as per PR recommendation
Peer Reviewer #7	Results	p 124 L-56 Unclear—was there no prevalence data based on eligible population? Was this not InterAction database?	Unclear as to specific section however entire KQ extensively rewritten and organized
Peer Reviewer #7	Results	p 125 L-24 Reword without "appears to be"	P136 (buttoned) or 160 (this final draft) changed as per PR recommendation
Peer Reviewer #7	Results	p 125 L-51 Is longitudinal the correct term?	P136 (buttoned) or 161 (this final draft) changed to long term as per PR recommendation
Peer Reviewer #7	Results	p 125 L-51 Is longitudinal the correct term?	As above
Peer Reviewer #7	Results	p 127 L-9 Does prevalence refer to treated (dx'd) prevalence?	P163 (p139 in final version draft) changed to diagnosed prevalence as per PR recommendation
Peer Reviewer #7	Results	p 127 L-17 country not county	Changed in version subsequent to PR version
Peer Reviewer #7	Results	p 127 L-20 Treated prevalence –more specific than method of ascertainment.	P163 p139 in final version draft) changed to diagnosed prevalence as per PR recommendation
Peer Reviewer #7	Results	p 127 L-18 How it is treated? Or extent to which it is treated?	KQ3 Key considerations rewritten and include treatment

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Results	p 127 L-29,30 Omit this bullet as it is not empirically derived	Unclear - no bullets there
Peer Reviewer #8	Results	d. Results: The amount of detail, characteristics of the studies, key messages, figures, tables, and appendices are well constructed, but somehow important publications from the last years were missing. James Swanson's 2006 and 2007 articles on the MTA concerning growth rates, latent class analyses, and propensity measures were not cited.	James Swanson: 2006 report is included in review {20945} 2007, there are two reports included in review {3227, 3228}
Peer Reviewer #8	Results	I find certain conclusions unusual, such as that on page 138 that the safety samples reported for atomoxetine equal those of guanfacine, a preparation approved for marketing a decade later. Atomoxetine's sponsor reported that its safety sample was well over 3,000 subjects. They had their million script written and have begun to unearth rare adverse events, such as jaundice. Did you find evidence of that number of subjects being exposed in the population to guanfacine?	Prevalence information completely organized and augmented from reading list from reviewer#7. ATX data rewritten but unable to identify this report to which this comment refers since by definition it would not meet screening criteria.
Peer Reviewer #8	Results	It is always difficult to include information that is relevant from data that is collected at the end of your time window for articles. However, it is becoming clearer now from analyses done in the 2007 Swanson papers on the MTA Sample, and more recent data, that growth effects may be a long term adverse event. By including the 2008 paper, the review would have been more balanced. The key paper by Molina et al in 2009 on the 8 year follow up of the MTA sample is also missing.	Swanson papers are included in review Molina paper is included in review
Peer Reviewer #8	Results	Another partial story is mentioned on page 135. There was an upsurge in use in Western Australia of stimulants, at least compared to the other states in Australia. In 2008, it was determined that this spike in exposure of children was due to four private practitioners who were running what amounted to medication mills. Similar high amphetamine prescribers were found in State of New York in the US when the triplicate prescription program was introduced. When the responsible physicians were identified and counseled, the rates of use of stimulants for ADHD in Western Australia quickly fell to the rates in the rest of the country.	Amended as per PR comments p160 Other world regions Sanfillipo, Calver, Preen et al. 100957 among others

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Results	You cite the worldwide prevalence of adult ADHD at 2.2%. What would have been helpful would have been to include the work of Ron Kessler using the US National Comorbidity Sample (Kessler et al; Amer J Psychiatry 163(4):716-23 and Arch Gen Psychiatry, 2010, Nov(11)1168-78. Your search criteria include articles about ADHD, and Kessler's work is not a meta-analysis but epidemiological prospective research, which should have met the other search criteria.	Kessler REFID 101714 p2 of executive summary and table 14 p148 and 153 (Kessler et al; Amer J Psychiatry 163(4):716-23 and Arch Gen Psychiatry, 2010, Nov(11)1168-78
Peer Reviewer #2	Discussion	The implications and importance of these questions are clearly stated. Directions for future research are also clearly stated, as well as public policy implications.	No response required.
Peer Reviewer #3	Discussion	Why on earth is there a section for suggestions for future research if the document is meant for health care decision makers like parents and practicing clinicians? How does this help them make better, more informed decisions?	The AHRQ will create versions of this report for different users.
Peer Reviewer #3	Discussion	Liked this section the best. Straight forward, well organized, summarized the evidence, and the issues with the evidence well.	No response required.
Peer Reviewer #4	Discussion	The recommendations for future research should include explorations of the effect of medication-induced appetite loss on nutritional balance, the possibility that ADHD meds may induce micronutrient wasting analogous to the vitamin B6, folate, B12, and D deficiencies induced by anticonvulsant drugs, and the interactions of nutritional supplementation with medication. (E.g, could nutritional supplementation reduce the optimal dose of stimulant for the same effect, thereby reducing side effects, as suggested by a couple of reports? I could provide a few refs if needed). These issues have significant implications for long-term treatment. A related issue is whether the mild growth slowing from stimulants, now confirmed in multiple reports, may be the tip of a safety iceberg for which we do not yet understand the hidden parts. (The growth loss itself is clinically insignificant for most patients, but could it be a marker for something more serious?) Finally, given the limitations of extant evidence-based treatments, there needs to be systematic, rigorous evaluation of the numerous alternative treatments being advocated, and creative development of new treatments, especially for preschoolers and adolescents.	See comments in executive summary and in limitations p 173 of 278
Peer Reviewer #5	Discussion	Reviewers thoroughly discuss implications of major findings as well as limitations of the review. I would like to have seen more regarding the 'pre-1990' context and studies.	More detail added to the beginning of the results section

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Discussion	Research section is easily translated into new research ideas.	No response required
Peer Reviewer #6	Discussion	Page 147 of 255: as already discussed – incorrect information regarding psychosocial adversity interfered with the effectiveness of adding psychostimulant medication to parent training in preschoolers with ADHD.	Rewritten ES-8, p44, Table 6,
Peer Reviewer #6	Discussion	Discussion/Conclusion: Overall, the discussion and conclusions are based on accurate synthesis of the literature. There are some concerns especially regarding key question 1 as detailed above in the results.	No response required
Peer Reviewer #7	Discussion	DISCUSSION SECTION p 128 L-21 Introduction change to: short-term effectiveness and safety...	Unclear – this is a table
Peer Reviewer #7	Discussion	p 128 L-26 long-acting guanfacine and clonidine; omit 2	Unclear – cannot find this phrase
Peer Reviewer #7	Discussion	p 128 L-32 For selected... omit: but not for all—very strong since nothing is 'for all'.	Not changed
Peer Reviewer #7	Discussion	p 128 L-42 other factors include clinician and family preferences.	Not changed – speaking of prevalence estimates, not treatment
Peer Reviewer #7	Discussion	p 129 L-17 remove “diminished over 2 years” or add to the medication intervention the expected length of impact e.g. L-20. Otherwise, there is a subtle bias toward medication—either oversimplifying long-term use to get symptom control or ignoring the PROBLEM of adherence altogether.	In summary of evidence added phrase about adherence to medication
Peer Reviewer #7	Discussion	p 129 L-28 atomoxetine over long periods of time: how long?	p.141, prg.1, removed phrase
Peer Reviewer #7	Discussion	p 129 L-29; also at p 130 L-51) maintain benefit despite discontinuation of medication following 12 months of use. There is no proportion of successful discontinuations and the extensive use across the age groups somewhat challenges this idea. Alternatively, some youth may 'outgrow' their symptoms (remission). Pharmacologically, there is no indication of effect beyond symptom control. And at p 130 L-33 maturation effect is then brought up.	p.141, prg.1, inserted maintain symptom benefit in table, difficult to include complexity of thought in the table, see discussion
Peer Reviewer #7	Discussion	p 129 L-31-32 Adverse events are better tolerated? Unclear what this sentence means.	Clarified that somnolence and fatigue are better tolerated

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Discussion	p 129 L-42 Spell out SES.	Changed as requested table 15 pg 164
Peer Reviewer #7	Discussion	Table 15. Adding references to the table would be most helpful as the summary tables are important and may be the only information readers have time to digest.	There is a reference attached to each citation in the tables.
Peer Reviewer #7	Discussion	p 130 L-7 Why is the term “adverse event outcomes” used instead of “safety”. It may be more precise but somewhat less eye-catching.	Changed to ‘safety’
Peer Reviewer #7	Discussion	p 130 L-14-18 unclear: in both clinical populations (ADHD and DBD)?	P165 changed to refer to <6 since DSM Dx not req'd for this group
Peer Reviewer #7	Discussion	p 131 L-11 parallel group	Unclear to what this refers – observation, request for clarification or word change? however section is extensively rewritten
Peer Reviewer #7	Discussion	p 132 L-29 ...use or in this subgroup have symptoms remit with maturation.	P167 Guanfacine paragraph changed as per PR comment
Peer Reviewer #7	Discussion	p 132 L-40 tolerance or loss of effectiveness... If the latter, switching to another stimulant might be a preferred alternative to reduce the risk of unnecessary ADEs from alpha-agonists.	p.144, last paragraph sentences adjusted to reflect issues raised.
Peer Reviewer #7	Discussion	p 132 L-50 Results of review of these studies are discussed below.	Inserted and checked to see that reference to MTA does occur below
Peer Reviewer #7	Discussion	p 132 L-58 First sentence is too strong: Perhaps: Short-term studies suggest medications...	P170 sentence less sweeping
Peer Reviewer #7	Discussion	p 133 L-30 Pls clarify what classes of ADHD meds are involved.	p.145, prg.4, changed to psychostimulants
Peer Reviewer #7	Discussion	p 133 L-47 But what proportion stay in treatment for these benefits?	p.145, prg.4, details not available, as results presented by group
Peer Reviewer #7	Discussion	p 134 L-12 Comparing US and Chinese doses and relating this to the intervention ignores the much greater sensitivity of Asians to western-population dosage. The doses are not expected to be equivalent.	p.146, first prg under Q3, sentence added to note genetic and cultural differences in samples
Peer Reviewer #7	Discussion	p 134 L-32 Are they longitudinal, i.e. in the same individuals over time?	p.146, prg.2, longitudinal has been added to first sentence in paragraph

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Peer Reviewer #7	Discussion	p 135 L-5 title is confusing as previously stated. Treated diagnostic prevalence, if defined, might be clearer than diagnosis (clinician ID) because it has been used in mental health epidemiology studies in the past. Also, prevalence of medication use should be separate from treated diagnostic prevalence.	p.147, Title is that okayed by TOO for KQ3
Peer Reviewer #7	Discussion	p 135 L-4 Unclear why “underlying prevalence of ADHD” is here. If this is ADHD diagnosed by clinicians in treated populations then it is the same as B on diagnosis. Does it belong in Section 2?	Because this is discussion of key questions and phrasing approved by AHRQ; otherwise it was changed in edition subsequent to PR draft
Peer Reviewer #7	Discussion	p 135 L-24 delete “most”	P172 section limitations, extended studies
Peer Reviewer #7	Discussion	p 135 L-32 ...as well as physician and family preferences and cultural variation.	P171section limitations, extended studies
Peer Reviewer #7	Discussion	p 135 L-39 Perhaps growth has slowed but considerably more youth are receiving stimulants so this emphasis on rate of increase is misleading. Ref 27,28 are old and 246 is based on parent report and flawed analysis (e.g. no Conf Intervals and selective endpoint to produce the result of “no difference”. Even if this is true of MEPS cohort it does not generalize to other data sources with greater statistical power.	p p.147, last paragraph, emphasis now reflects ongoing increases in medication use rather than rates of increase
Peer Reviewer #7	Discussion	p 135 L-41 how much lower? ?-x-fold in Germany and half as likely in the Netherlands.	Relative use in Europe and US has been clarified
Peer Reviewer #7	Discussion	p 135 L-43 change receive to “have dispensed medication...”	Changed text
Peer Reviewer #7	Discussion	p 136 L-4-5 Again the focus on short-term effects for psychosocial interventions when medications only improve symptoms—do not ‘cure’ ADHD or maintain effects without regular use.	p.148, text adjusted to reflect issues regarding duration of treatment
Peer Reviewer #7	Discussion	p 136 L-18 short-term trial; then L-22 long-term effectiveness and safety: inconsistent. Remove s from interventions	p.148, Transition in topic clarified
Peer Reviewer #7	Discussion	p 136 L-26-30 Limitation is confusing in relation to poor findings. Usually we refer to limitations of design and methods, n’est pas?	p.148, ‘limitation’ is consistent with the rest of document.
Peer Reviewer #7	Discussion	p 137 L-39 Add regional and parent-preferences	Discussion added

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Peer Reviewer #7	Discussion	p 137 L-40 add ...treated diagnostic prevalence...	Added to discussion
Peer Reviewer #7	Discussion	p 137 L-57 add foster care as a vulnerable group	Added to discussion
Peer Reviewer #7	Discussion	p 138 L-7 statement on “administrative and prescription databases” could be clearer as administrative claims include information on diagnostic, dispensed prescription drugs and enrollee characteristics. Other prescription databases may only permit sales information with most patient variables and projections from surveyed data.	p.149, description of databases expanded
Peer Reviewer #7	Discussion	p 138 L-21 There is no mention of the impact of comorbidities and resulting concomitant drug therapy on the overall benefit/risk of rx treatments for ADHD. Also, the relatively lower persistence of use in non-white and low income youth needs further attention.	p.149, non-white and low income youth mentioned in discussion of patient preferences
Peer Reviewer #7	Discussion	p 139 L-34 Third bullet grammar is not consistent with others.	Changed wording order
Peer Reviewer #7	Discussion	p 139 L-39 the word ‘sectoral’ is confusing. I read it as a misspelling of sectional. Perhaps, across-sector would be clearer.	Changed to across-sector
Peer Reviewer #7	Discussion	p 139 L-44 Investigations of...	Changed to Investigations of
Peer Reviewer #7	Discussion	p 139 L-53 long-acting guanfacine and clonidine...	Changed spelling of Guanfacine
Peer Reviewer #7	Discussion	p 139 L-58 to p 140 L-4 references for discontinuation trials	References for specific results are in the section describing the results
Peer Reviewer #7	Discussion	p 140 L-7 Conclusions and Recommendations Unresolved questions of long-term benefits remain.	Unclear; however this section has been extensively rewritten and amplified
Peer Reviewer #7	Discussion	p 140 L-25 relapse prevention? Is this the #1 priority? Complicated by the assumption of long-term use as necessary.	The question is long term effects, relapse indicates the effectiveness of treatment
Peer Reviewer #7	Discussion	p 140 L-10 data are...	Changed to data are

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Peer Reviewer #7	Discussion	p 140 L-33 How about other comorbidities e.g. depression?	Added text
Peer Reviewer #7	Discussion	p 140 L-49 More objective outcomes, e.g. reduced criminal or court-related events; fewer days of psychiatric hospitalizations or number of hospitalizations; improved academic performance. Essentially, don't we want distal outcomes as well as proximal outcomes?	Added text
Peer Reviewer #7	Discussion	p 140 L-53 Rigorous observational (cohort) research through efficient data collection, e.g. from Electronic Medical Records enhanced by collection of reliable information of satisfaction, persistence, and proximal and distal outcomes.	Added text to list
Peer Reviewer #7	Discussion	p 141 L-6 treated diagnostic prevalence	P153 inserted 6 lines under table 14 (as it was called when this was responded to.
Peer Reviewer #7	Discussion	p 141 L-11 sentence on methodological issues does not acknowledge the differences in regional, cultural, ethnic, national, physician specialty and parent preference.	70/273 these issues added to summary of KQ3 and to discussion
Peer Reviewer #7	Discussion	p 141 L-17,18 overemphasis on slowed use (as previously noted)	Adjusted throughout KQ3
Peer Reviewer #7	Discussion	p 141 L-39 Why is this cross-sector data uniquely required in ADHD? Wouldn't it be useful for other mental health conditions in youth? Treatment of depression or anxiety for example	Changed to especially
Peer Reviewer #7	Discussion	p 141 L-40 Add comorbidities and resulting concomitant use to needed research on community practice patterns.	Added 'other comorbidities' to point in list

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Peer Reviewer #8	Discussion/ Conclusion	<p>e. Discussion/ Conclusion: Though this is a modern review, some of the conclusions seem based on earlier reports. For example, you conclude that the use of stimulants peaked in 2000. What was this based upon?</p> <p>Your data on stimulant use in Canada appears to be 8 years old, even before Health Canada imposed a one year ban on the marketing of Adderall XR. Why use the older data?</p> <p>Overall, I find the studies included were described adequately, and you were most generous in rating them as strongly as you did.</p> <p>However, I believe that the investigators omitted several important publications, particularly those that occurred after 2006. One missing comparative RCT published in a leading peer reviewed journal had a pharmaceutical sponsored publication reporting that the comparator drug beat their product (OROS was more effective than atomoxetine)!</p>	<p>Buitelaar {469} was a meta-analysis, excluded Starr paper {106646} did not meet inclusion criteria, subjects were not ≤ 6 years and the total treatment and followup time was <12 months. (OROS vs Atomoxetine)</p> <p>Newcorn and Michaelson 2007 {1941} added to section in final discussion on Atomoxetine.</p> <p>These points are addressed in the re-vamped document</p>