

AHRQ Comparative Effectiveness Review Surveillance Program

CER #44: Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment

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Summary of Key Findings:

- For Key Question 1, studies were identified suggesting that conclusions on the long-term effectiveness of multicomponent interventions are possibly out of date, and that conclusions on adverse events related to MPH are possibly out of date.
- For Key Question 2, conclusions on adverse events related to MPH and ATX are possibly out of date due to adverse events due to safety concerns identified in the previous surveillance assessment, and are possibly out of date for height and weight due to an identified study. Conclusions for LDX are out of date due to no identified studies in the original CER and one identified study. Conclusions for parent behavior training are possibly out of date.
- For Key Question 3, previous surveillance and studies identified suggest that conclusions regarding prevalence by geography and sex in adults are possibly out of date, that conclusions related to prevalence by age are out of date, and that conclusions of prevalence by race/ethnicity are probably out of date. Conclusions related to treatment by geography, SES, sex, and age are possibly out of date due to previous surveillance and identified studies.

Signal Assessment: The signals examined in this surveillance assessment suggest that the original CER is possibly out of date.

Authors:

Karli Kondo

Maya O'Neil

Shammarie Mathis

Ryan McKenna

Kelly Vander Ley

Johanna Anderson

Mark Helfand

Conflict of Interest:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Reviewers

Julie Zito, PhD
Professor of Pharmacy and Psychiatry
Pharmaceutical Health Services Department
University of Maryland, Baltimore
Baltimore, MD

Stephen Faraone, PhD
Distinguished Professor of Psychiatry and Behavioral Sciences
Professor of Neuroscience and Physiology
Departments of Psychiatry and Neuroscience & Physiology
SUNY Upstate Medical University
Syracuse, NY

Alice Charach, MD, FRCPC
Hospital for Sick Children
Head, Neuropsychiatry Team
Department of Psychiatry
University of Toronto
Toronto, ON

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Introduction

The purpose of the surveillance process for the EPC Program is to decide if and when a systematic review is in need of updating. Approximately 25 systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #44 titled “Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment” was originally released in October 2011.¹ Surveillance assessment was completed in July, 2012 at which time the CER’s priority for updating was low.²

The key questions for the original CER are as follows:

Key Question 1: Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

Key Question 2: Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of follow up or treatment, including, but not limited to, 12 months or more of continuous treatment?

Key Question 3: How do: (a) underlying prevalence of ADHD, and (b) rates of diagnosis (clinical identification) and treatment of ADHD vary by geography, time period, and by sociodemographic characteristics?

Our surveillance assessment began in May, 2014. We conducted an electronic search for literature published since the most recent surveillance report search date. After completing a scan of this literature to identify evidence potentially related to the key questions in this CER, we contacted experts involved in the original CER to request their opinions as to whether the conclusions had changed.

Methods

Prior Surveillance

A surveillance report for the original CER was released in July, 2012, and included a search for relevant literature published between January 2010 and June 2012, expert opinion, and a search of FDA reports.² The findings from this report are included in our assessment.

Literature Searches

We conducted three literature searches of PubMed and PsycINFO using the identical search strategy used for the original report.¹ We conducted two searches to assess the signal for update; the first June 2010 to May 2014, and the second June 2012 to May 2014, to look specifically at the time period since the

previous surveillance report. The last search covered June 2012 to May 2014, and was conducted to assess the size and feasibility of a systematic review.

The first and second searches were conducted to assess a signal for the potential to update. This process included selecting journals from among the top 10 journals from relevant specialty subject areas (Appendix A) and among those most highly represented among the references for the original report (Appendix B). These searches included the same nine journals selected for the prior surveillance assessment (Annals of Internal Medicine, Behavior Modification, The British Medical Journal, Journal of Abnormal Child Psychology, Journal of the American Medical Association, Journal of Child Psychology and Psychiatry, Journal of Clinical Child and Adolescent Psychology, Lancet, New England Journal of Medicine), plus one additional high-impact journal (Cochrane Database Systematic Reviews) and twelve specialty journals (Child Development, Developmental Psychology, Pediatrics, American Journal of Psychiatry, Journal of Clinical Psychiatry, Journal of Child and Adolescent Psychopharmacology, Journal of the American Academy of Child and Adolescent Psychiatry, European Child and Adolescent Psychiatry, Journal of Attention Disorders, Archives of General Psychiatry, Archives of Pediatric and Adolescent Medicine, and Journal of Developmental and Behavioral Pediatrics).

The third search was conducted to assess the volume of literature and size of a potential systematic review. The second search included a full search of Pubmed and PsycINFO. The search strategy is reported in Appendix C.

Study Selection

Using the same inclusion and exclusion criteria as the original CER (see Appendix D), one investigator reviewed the titles and abstracts of the 22 high-impact journal search results (Appendix E).

To calculate the expected number of included studies based on the total number of studies resulting from the full search, a random sample of 200 titles and abstracts resulting from the full search were reviewed for inclusion.

Expert Opinion

We shared the conclusions of the original report and the newly identified studies with seven experts in the field (original peer reviewers, technical expert panel members [TEP] and a local expert) to request their assessment of the need to update the report and their recommendations of any relevant new studies. Three subject matter experts responded to our request. Appendix F shows the forms that were sent to the experts. Note that Annals of Internal Medicine, Behavior Modification, and Journal of Clinical Child and Adolescent Psychology were added to the included list of searched journals after summaries were shared with expert reviewers. Consequently, expert reviewers did not receive information on the one article³ meeting inclusion criteria that were published in these journals.

Horizon Scanning High-Impact Potential

The AHRQ Healthcare Horizon Scanning System identifies emerging health care technologies and innovations with the potential to impact health care for AHRQ's 14 priority conditions.⁴ We reviewed the topics in the Depression and Other Mental Health Disorders priority area for potentially high-impact interventions⁵ related to the key questions in this CER. Potentially high impact interventions were considered in the final assessment of the need to update.

FDA Black Box Warnings

We searched the FDA MedWatch online database website for black box warnings relevant to the key questions in this CER.

Check for qualitative signals

The authors of the original CER conducted a meta-analysis on the efficacy of parent behavior training for Disruptive Behavior Disorder (DBD) in preschoolers. They performed qualitative syntheses on the effectiveness of other interventions for children less than six years of age with Attention Deficit Hyperactivity Disorder (ADHD), and the associated adverse events following treatment, as well as the effectiveness and adverse events associated with twelve months or more of treatment for people six years and older with ADHD, and differences in the prevalence, rates of diagnosis, and treatment by geography, time period, provider type and sociodemographic characteristics. We compared the conclusions of the included abstracts to the conclusions of the original CER and surveillance reports, and assessed expert opinions to identify qualitative signals to update.

Compilation of Findings and Conclusions

For this assessment we constructed a summary table (Appendix G) that includes the key questions, the conclusions from the original CER and most recent surveillance assessment, findings of the new literature search, and the expert assessments that pertained to each key question. Because we did not find any FDA black box warnings relevant to the key questions in this CER, we did not include a column for this in the summary table. We categorized whether the conclusions need updating using a 3-category scheme:

- Original conclusion is still valid and this portion of the CER is likely not in need of updating
- Original conclusion is possibly out of date and this portion of the CER may need updating
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as likely not in need of updating.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

Signal Assessment for Updating

We used the following considerations in our assessment of the need to update this CER:

- **Strong signal:** A report is considered to have a strong signal for updating if new evidence is identified that clearly renders conclusions from the original report out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal for updating when new evidence is identified which may change the conclusions from the original report. This may occur when abstract review and expert assessment indicates that some conclusions from the original report may be out of date, or when it is unclear from abstract review how new evidence may impact the findings from the original report. In this case, full-text review and data abstraction may be needed to more clearly classify a signal.
- **Weak signal:** A report is considered to have a weak signal for updating if little or no new evidence is identified that would change the conclusions from the original report. This may occur when little to no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original report.

Results

Prior Surveillance

Prior surveillance of the topic included 16 studies and consultation with six subject matter experts, and concluded that for Key Question 1, the conclusions on adverse events for methylphenidate (MPH) were possibly out of date due to new FDA data, that for Key Question 2 the conclusions on adverse events were possibly out of date due to new FDA data on adverse events associated with MPH due to new FDA data, and UK Medicines and Healthcare products Regulatory Agency (MHRA), and Health Canada warnings regarding atomoxetine (ATX) and increased blood pressure, although they found two studies reporting no risk of serious cardiovascular events in the general population. For Key Question 3, conclusions regarding prevalence in adults by sex were probably out of date, and prevalence by age was probably out of date. All other original CER conclusions were determined to be up to date.²

Literature Searches

The literature search from June 2012 to May 2014 identified 5,612 unique titles, with 796 from the 22 selected high profile general medical and specialty journals. A random selection of 200 articles from the 22 selected high profile general medical and specialty journals is provided in Appendix E. After title and abstract review, 764 studies were rejected because they did not meet the original CER inclusion criteria (see Appendix D). The remaining 15 studies^{3; 6-19} were examined for potential to change the results of the original review. From the remaining 4,816 titles, a random sample of 200 (100 MEDLINE and 100 PsycINFO) were reviewed for inclusion. None of the MEDLINE and 4% of the PsycINFO titles met criteria for inclusion for an expected total of 80 studies.

Horizon Scanning

The topic the horizon scanning report for Priority Area 05: Depression and Other Mental Health Disorders⁵ identified was *Off-label intranasal oxytocin for treatment of social dysfunction in autism spectrum disorders*. This intervention does not cover any of the key questions in this report, thus there is no high-impact potential for this CER.

FDA Black Box Warnings

We did not find any FDA black box warnings relevant to the key questions in this CER.

Expert Opinion

We shared the conclusions of the original report with thirteen experts in the field (original peer reviewers, TEP members, the original CER investigator, and a local expert) to request their assessment of the need to update the report and their recommendations of any relevant new studies. Three subject matter experts responded. Appendix F shows the forms that were sent to the experts.

While the experts agreed that most of the conclusions in the original CER were up to date, all three experts identified at least one conclusion in the report they believed to be out of date (see Appendix G).

Identifying Qualitative Signals

Appendix G shows the original key questions, the conclusions of the original report, the results of previous surveillance assessment², the literature, the experts' assessments, and the recommendations of the Scientific Resource Center (SRC) regarding the need for update.

Signal Assessment for Updating

A number of the studies we identified have the potential to change the conclusions in the original CER. For Key Question 1, the original report identified no studies extending beyond 70 weeks examining the long-term effectiveness of multicomponent interventions.¹ For studies of two years or less, the original CER concluded that the relative benefits of school-based interventions diminish. We identified a six year follow up study to the Preschool ADHD Treatment Study (PATS), that found that parent and teacher rated severity decreased from baseline to year three, then remained stable in the moderate to severe clinical range through year 6. Girls showed generally steeper decreases in symptom T-scores. At year 6, 89% (160/180) of remaining participants met ADHD symptom and impairment diagnostic criteria.⁶ In addition, we found a one year follow up study of the Incredible Years interventions, which found that 22 of 27 variables that showed post-treatment effects were maintained, with 70-75% falling below clinical cutoffs for externalizing behaviors (50% at baseline), and more than 50% fell below clinical cutoffs for hyperactivity and inattentiveness (all in clinical range at baseline).³

For Key Question 2, the original CER concluded that MPH and ATX are generally well tolerated and provide control of ADHD for months to years at a time. We identified a study conducted in Norway which surveyed adults who had been treated with ADHD medication and found that pharmacologic treatment for more than two years was associated with better functioning (Adult ADHD Self-Report Scale and Mental Health Index-5) than treatment for two years or less.⁷ Another identified study in Italy examining the long term effects of MPH or ATX on growth in ADHD drug naïve children found that both ATX and MPH lead to decreased height gain, with a significantly higher effect for ATX than for MPH; however, the difference between groups was only significant during the first year of treatment. For both ATX and MPH there was a slowed rate of weight gain for both drugs that was significantly higher for

ATX than MPH⁸, and another study examining cardiovascular effects of ATX and MPH performed blood pressure, heart rate, and ECG assessments at six month intervals for 24 months and increases in blood pressure and heart rate at 6 and 12 months with both ATX and MPH, with a higher probability for MPH.⁹ In addition, the original CER included no studies evaluating lisdexamfetamine dimesylate (LDX). We identified a one-year study of the safety and effectiveness of LDX in adolescents who found improvement on the YQOL-R and ADHD-RS-IV, and had no significant EEG or vital sign changes.¹⁰ With regard to long-term effects of combined treatment in persons six and older, the original CER concluded insufficient evidence for parent behavioral training. We identified a study comparing MPH to MPH + parent training that examined participants at one-year follow up and found that there were no significant effects associated with the addition of parent training.¹¹

For Key Question 3, with respect to prevalence, by geography, the original CER concluded that the underlying prevalence does not appear to vary much between nations and regions, once differences in methodologies for ascertainment are taken into account. We identified a study examining the prevalence of ADHD in Lebanon that found that the prevalence of ADHD Inattentive subtype was 3 per 1,000; Hyperactive-Impulsive subtype 12 per 1,000; and ADHD Combined subtype 17 per 1,000¹², and an analysis of data from the National Survey of Children's Health 2003-2011 identified by one of our experts found that fewer children in the West under 18 had ever been diagnosed (8.1%), had a current diagnosis (6.4%), with the highest rates in the South (12.6%; 10.1%).¹³ By time period, the original CER concluded that the prevalence of cases of ADHD has increased since 1902. Consistently, data from the National Survey of Children's Health 2003-2011 found that between 2003 and 2011, ADHD diagnoses increased from 7.8% to 11% for those ever diagnosed, and 7.2% in 2007 to 8.8% in 2011 for current diagnoses.¹³ By socioeconomic status (SES), the original CER concluded that those of lower SES have a higher prevalence of ADHD. Consistently, data from the National Survey of Children's Health 2003-2011 found that rates of ADHD were highest in households below the federal poverty level, and lowest in those greater than 200% of the federal poverty level. Rates were the highest among those living in households with 12 years of education (higher than both more and less education), with the lowest rates from households with less than 12 years. Rates were significantly higher among children with any healthcare coverage, with the highest rates among those covered by Medicaid. By sex, the original CER concluded that males have a higher prevalence of ADHD than females. We identified a study of the Early Childhood Longitudinal Study found¹⁴ that being male increased the risk of an ADHD diagnosis. Another study found that in Germany, the standardized age prevalence and incidence of new diagnoses were 3-4 time higher for males than females 3-17 years old¹⁵, and data from the National Survey of Children's Health 2003-2011 found that males were more likely to have a current or previous diagnosis.¹³ By age, the original CER conclude that children 5-10 years old appear to experience the highest prevalence. Data from the National Survey of Children's Health 2003-2011 found that among children under 18, those aged 4-10 had the lowest rates of ever being diagnosed with ADHD (7.7%), having a current diagnosis (6.8%), with the highest rates among 11-14 year olds (14.3%; 11.4%). By race/ethnicity, the original CER concluded that prevalence rates are lower in African American and Hispanic children as compared with Whites. We identified a study that study found that being White and being raised in an English-speaking household increased the risk of an ADHD diagnosis¹⁴, and another study of children aged 5-11 years at Kaiser in Southern California found that children diagnosed with ADHD were more likely to be White or African American.¹⁶ Further, data from the National Survey of Children's Health 2003-2011 found that rates were similar between White and Black children under 18, and significantly higher than all other

rates. Rates in Hispanic/Latinos were significantly lower than non-Hispanic/Latinos. Rates were significantly higher among those who spoke English at home.¹³

For treatment, by location, the original CER concluded that geographical regions show little significant variation ranging from higher use in the South than in the West. Data from the National Survey of Children's Health 2003-2011 found larger differences in medication treatment in children in the West (3.8%) as compared with those in the South (7.3%).¹³ By time, the original CER concluded that the rate of psychostimulant medication has increased over the past 3 decades. Data from the National Survey of Children's Health 2003-2011 found that between 2007 and 2011, rates of medication for ADHD increased from 4.8% to 6.1%.¹³ By SES, the original CER found that children of higher SES were more likely to receive medication, and that insurance status may influence access. Data from the National Survey of Children's Health 2003-2011 found that children under 100% (PR = 1.22) and between 100-200% (PR = 1.16) of poverty were more likely to be treated with medication than children >200% of poverty, and children receiving public health insurance (PR = 1.52) were more likely to be treated than those with private insurance, with uninsured children the least likely to be treated (PR = 0.42).¹³ By sex, the original CER concluded that only sparse comparative data were available examining rates of treatment by sex once ADHD is diagnosed. We identified one study that found that in Germany, there was little difference in drug treatment among females and males 3-17 years old,¹⁵ and another German study examining usage patterns of MPH and ATX found that drug treatment was more common in boys than girls and that girls discontinued treatment earlier than boys.¹⁷ Congruently, the National Survey of Children's Health 2003-2011 found that males were 2.31 times more likely to be treated with medication.¹³ By age, the original CER concluded that medication treatment prevalence is higher for primary school-age children than for adolescents or adults. We found a study in Iceland that examined age within grades, and found that children in the youngest third of class were 50% more likely (1.5; 95% CI 1.3-1.8) than those in the oldest third to be prescribed stimulants between ages 7 and 14,¹⁸ and data from the National Survey of Children's Health 2003-2011 found that among children under 18, those aged 4-10 had the lowest rates of currently being on medication for ADHD (4.9%), with the highest rates among 11-14 year olds (8.0%).¹³ By race/ethnicity, the original CER concluded that Caucasian children are twice as likely to use stimulants as either Hispanic or African American children, and minority ethnicity is associated with shorter duration of medication use. We found one study that analyzed FL Medicare claims data and found that despite equivalent switching to long-acting medications in the study period, minorities continued to utilize all ADHD medications less than did whites, and for shorter periods, and another study of children aged 5-11 years at Kaiser in Southern California which found that children who had received more than two prescriptions specific to ADHD were more likely to be White or African American.¹⁶ Data from the National Survey of Children's Health 2003-2011 found that medication rates were lower in Black (0.80) and other racial minorities (0.50) as compared with Whites, and that rates were significantly higher in Whites than in Hispanics (PR = 0.44) and children whose primary language at home was not English (PR = 0.14).¹³

The SRC recommendation based on the results of the prior surveillance assessment, recent literature, FDA boxed warning information, horizon scanning, ongoing clinical trials, and expert assessment is that:

- Key Question 1: Conclusions on the long-term effectiveness of multicomponent interventions are possibly out of date due to the studies included in the original CER being limited to 70 months,

and an identified 6-year follow up study. Conclusions on adverse events related to MPH are possibly out of date with regard to safety concerns identified in the previous surveillance assessment.

- Key Question 2: Conclusions on adverse events related to MPH and ATX are possibly out of date due to adverse events due to safety concerns identified in the previous surveillance assessment and possibly out of date for height and weight due to an identified study that found decreased height gain and a slowed weight gain. Conclusions for LDX are out of date due to no identified studies in the original CER and one study that found improvement on the YQOL-R and ADHD-RS-IV and no significant EEG or vital sign changes. Conclusions for parent behavior training are possibly out of date due to a study that found no significant effect associated with the addition of parent training to MPH, with the original CER concluding that insufficient evidence for parent behavioral training.
- Key Question 3: Conclusions regarding prevalence by geography are possibly out of date due to original CER conclusions that prevalence does not vary much between regions once methodologies for ascertainment are taken into account, and a national study that found higher rates in the South and lower rates in the West. Conclusion on prevalence by sex in adults is possibly out of date due to findings related to adults in the previous surveillance assessment. Conclusions related to prevalence by age of greater prevalence in children ages 5-10 are out of date due to findings from the previous surveillance assessment and a study that congruently found greater prevalence in 11-14 year olds. Conclusions that prevalence rates are lower in African American and Hispanic children as compared with Whites are probably out of date due to two studies that found higher and similar rates in African American and White children. Conclusions related to treatment by geography, that while treatment rates are higher in the South than the West, differences are small and non-significant, are possibly out of date, due to a study that found larger differences between treatment rates in the South and the West. Conclusions related to treatment by SES, with medication treatment more likely in higher SES, are possibly out of date due to a study that found lower rates of medication treatment in low-income and poverty populations, and children without health insurance. Conclusions related to treatment by sex, that sparse data exists, are possibly out of date due to a study that found little difference by sex, and two studies that found higher rates of medication treatment in boys. Conclusions related to treatment by age, that primary school aged children have the highest rates of treatment, are possibly out of date, due to a study that found higher rates of medication in 11-14 year olds.

The signal to update this report is medium, suggesting that the conclusions in the original report are possibly out of date.

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Appendices

Appendix A: Top 10 Journals

Appendix B: Most Cited Journals from Original Systematic Review

Appendix C: Original Search Strategy

Appendix D: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix E: Literature Search Results

Appendix F: Questionnaire Sent to Expert Reviewers

Appendix G: Summary Table

Appendix A. Top 10 Journals

In the Journal Citation Reports database, the science and social science sections were searched by subject area discipline(s) for each surveillance reports topic area (e.g., second generation anti-depressants in adults retrieved top 10 lists from behavioral sciences, psychiatry, and psychology respectively). For each subject area discipline, the list was constructed by selecting the top 10 journals from the five year citation impact factor average list. Selected citations were downloaded in .csv format.

Behavioral Sciences:

1. Behavioral & Brain Sciences
2. Trends
3. Neuroscience & Biobehavioral Reviews
4. Advances in the Study of Behavior
5. Cognitive, Affective, & Behavioral Neuroscience
6. Frontiers in Behavioral Neuroscience
7. Cortex
8. Autism Research
9. Neuropsychologia
10. Biological Psychology
11. Behavioral & Brain Sciences

Psychiatry:

1. Archives of General Psychiatry
2. American Journal of Psychiatry
3. Journal of Molecular Psychiatry
4. Biological Psychiatry
5. Schizophrenia Bulletin
6. Neuropsychopharmacology
7. Journal of the American Academy of Child Psychiatry
8. British Journal of Psychiatry
9. Journal of Psychiatry and Neuroscience
10. World Psychiatry

Developmental Psychology:

1. Autism Research
2. Child Development
3. Developmental Psychology
4. Development & Psychology
5. Developmental Review
6. Developmental Science
7. Journal of Abnormal Psychology
8. Journal of the American Academy of Child Psychology
9. Journal of Autism and Developmental Disorders
10. Journal of Child Psychology & Psychiatry

Pediatrics Top 10:

1. Journal of the American Academy of Child Psychiatry
2. Pediatrics
3. Archives of Pediatric & Adolescent Medicine
4. Journal of Pediatrics – US
5. Developmental Disabilities Research Reviews
6. Journal of Adolescent Health
7. Seminars in Fetal and Neonatal Medicine
8. Archives of Disease in Childhood – Fetal and Neonatal Edition
9. The Pediatric Infectious Disease Journal
10. Developmental Medicine & Child Neurology

Educational Psychology:

1. Child Development
2. Journal of Educational Psychology
3. Educational Psychology Review
4. Educational Psychology – US
5. Contemporary Educational Psychology
6. Learning and Instruction
7. Journal of School Psychology
8. Journal of Counseling Psychology
9. Journal of Learning Sciences
10. School Psychology Review

Psychology:

1. Annual Review of Psychology
2. Psychological Bulletin
3. Annual Review of Clinical Psychology
4. Psychological Review
5. Social Cognitive and Affective Neuroscience
6. Journal of Child Psychology and Psychiatry
7. Psychological Medicine
8. Psychotherapy and Psychosomatics
9. Cognitive Psychology
10. Health Psychology

Special Edition:

1. Research in Autism Spectrum Disorders
2. Exceptional Children
3. Journal of Fluency Disorders
4. Research in Developmental Disabilities
5. Journal of Positive Behavior Interventions
6. American Journal on Intellectual and Developmental Disabilities
7. Journal of Learning Disabilities – US
8. Journal of Special Education
9. Journal of Emotional and Behavioral Disorders
10. Annals of Dyslexia

Top 10 General Medical:

1. The New England Journal of Medicine
2. Lancet
3. Journal of the American Medical Association
4. PLoS Medicine
5. Annals of Internal Medicine
6. British Medical Journal
7. Archives of Internal Medicine
8. Canadian Medical Association Journal
9. Cochrane Database of Systematic Reviews
10. BMC Medicine

Appendix B. Most Cited Journals from Original Systematic Review

Journal	Citations
Journal of the American Academy of Child and Adolescent Psychiatry	43
Journal of Child and Adolescent Psychopharmacology	17
Pediatrics	15
Journal of Abnormal Child Psychology	12
American Journal of Psychiatry	8
European Child & Adolescent Psychiatry	8
Journal of Attention Disorders	8
Journal of Child Psychology and Psychiatry	7
Archives of General Psychiatry	5
Archives of Pediatrics and Adolescent Medicine	5
Journal of Developmental & Behavioral Pediatrics	5
Biological Psychiatry	4
Journal of Clinical Child & Adolescent Psychology	4
Journal of Consulting and Clinical Psychology	4
School Psychology Review	4
The British Journal of Psychiatry	3
Canadian Journal of Psychiatry	3
Child and Adolescent Psychiatry Mental Health	3
Psychiatric Services	3
American Journal of Orthopsychiatry	2
Ambulatory Pediatrics	2
Annals of Pharmacotherapy	2
Archives of Iranian Medicine	2
Behavior Change	2
Behavioural and Cognitive Psychotherapy	2
Behavior Therapy	2
British Medical Journal	2
Child & Adolescent Psychiatric Clinics of North America	2
Clinical Pediatrics – Phila	2
Clinical Neuroscience Research	2
CNS Spectrums	2
Journal of Clinical Psychiatry	2
Journal of Health Economics	2
Journal of Managed Care Pharmacy	2
Journal of Paediatrics and Child Health	2
Journal of Pediatrics	2
Journal of Pediatric Psychology	2
Psychopharmacology Bulletin	2

Appendix C. Original Search Strategy

Medline via Ovid searched on June 6, 2014

Limited to January 2010 to present

Limited to the following journals:

- *American Journal of Psychiatry*
- *Archives of General Psychiatry*
- *Archives of Pediatric and Adolescent Medicine*
- *British Medical Journal*
- *Child Development*
- *Cochrane Library of Systematic Reviews*
- *Journal of Developmental and Behavioral Pediatrics*
- *Developmental Psychology*
- *European Child and Adolescent Psychiatry*
- *JAMA*
- *Journal of Abnormal Child Psychology*
- *Journal of Attention Disorders*
- *Journal of Child Psychology and Psychiatry and allied disciplines*
- *Journal of Child & Adolescent Psychopharmacology*
- *Journal of Clinical Psychiatry*
- *Journal of the American Academy of Child & Adolescent Psychiatry*
- *Lancet*
- *New England Journal of Medicine*
- *Pediatrics*
- *Annals of internal Medicine*
- *Behavior Modification*
- *Journal of clinical child & adolescent Psychology*

Search String(s)

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to May Week 4 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 05, 2014>

Searched June 6th 2014

Search Strategy from Original Report 1 "attention deficit and Disruptive Behavior Disorders"/ or attention deficit disorder with hyperactivity/ or Conduct Disorder/ (22899)

- 2 minimal brain d?sfuction*.tw,sh. (537)
- 3 (attention deficit* or adhd).ti. (13052)
- 4 addh.tw. (114)
- 5 or/1-4 (24361)
- 6 Hyperkinesis/ (3690)
- 7 Impulsive Behavior/ (5365)
- 8 Child Behavior Disorders/ (18392)
- 9 aggression/ or agonistic behavior/ (27568)
- 10 inattent*.tw. (4462)
- 11 Impulse Control Disorders/ (2031)
- 12 (disruptive adj4 disorder?).tw. (1122)
- 13 or/6-12 (58520)
- 14 limit 13 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") (10357)
- 15 exp *Mental Disorders/ (782251)
- 16 (attention deficit* or adhd).tw. (21089)
- 17 hyperactiv*.tw. (38280)
- 18 inattent*.tw. (4462)
- 19 Impulsive Behavior/ (5365)
- 20 or/16-19 (49372)
- 21 15 and 20 (23568)
- 22 5 or 21 (32199)
- 23 limit 22 to yr="2010 -Current" (9898)
- 24 14 or 23 (19782)
- 25 Drug Therapy/ae, co, ct, mo (254)
- 26 (side effect? or adverse or harm?).tw. (469153)

- 27 atomoxetine.tw. (957)
- 28 guanfacine.tw. (714)
- 29 Lisdexamfetamine.tw. (151)
- 30 Vyvanse.tw. (21)
- 31 exp Central Nervous System Stimulants/ae, ct, po, to (11497)
- 32 ritalin.tw. (604)
- 33 or/25-32 (481239)
- 34 (attention deficit* or adhd).tw. (21089)
- 35 33 and 34 (2952)
- 36 24 or 35 (21722)
- 37 (comment or editorial or letter).pt. (1338065)
- 38 36 not 37 (20902)
- 39 review.pt,sh. (1882226)
- 40 38 and 39 (2490)
- 41 meta-analysis.pt,ti,ab,sh. (70326)
- 42 (meta anal\$ or metaanal\$).ti,ab,sh. (85554)
- 43 ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ti. (37551)
- 44 ((methodol\$ or systematic\$ or quantitativ\$) adj3 (review\$ or overview\$ or survey\$)).ab. (55224)
- 45 ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab. (14426)
- 46 (medline or embase or cochrane).ti,ab. (72202)
- 47 or/44-46 (119741)
- 48 review.pt,sh. (1882226)
- 49 47 and 48 (70921)
- 50 41 or 49 or 43 or 42 (143255)

	51	38 and 50 (615)
	52	40 not 51 (2119)
	53	38 not 52 (18783)
	54	limit 53 to humans (17175)
	55	limit 54 to english language (15645)
Journal Limits	56	"american journal of psychiatry".jn. (23881)
	57	"archives of general psychiatry".jn. (8254)
	58	"archives of pediatrics & adolescent medicine".jn. (4554)
	59	british medical journal.jn. (97278)
	60	child development.jn. (5772)
	61	"cochrane database of systematic reviews".jn. (10848)
	62	developmental psychology.jn. (2262)
	63	european child & adolescent psychiatry.jn. (1325)
	64	jama.jn. (65409)
	65	"journal of abnormal child psychology".jn. (2317)
	66	"journal of attention disorders".jn. (646)
	67	"journal of child psychology & psychiatry & allied disciplines".jn. (3788)
	68	"journal of child & adolescent psychopharmacology".jn. (1353)
	69	"journal of clinical psychiatry".jn. (9377)
	70	"journal of the american academy of child & adolescent psychiatry".jn. (5609)
	71	lancet.jn. (128610)
	72	"new england journal of medicine".jn. (70874)
	73	pediatrics.jn. (31541)
	74	"journal of developmental & behavioral pediatrics".jn. (2252)
	75	"annals of internal medicine".jn. (20466)

- 76 behavior modification.jn. (1014)
- 77 "journal of clinical child & adolescent psychology.jn. (1053)
- 78 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 (489514)
- 79 55 and 78 (26828)
- Date Limits 80 limit 76 to yr="2010-current" (1719)

Database: PsycINFO <1806 to May Week 4 2014>

Searched June 6th, 2014

Search Strategy from Original Report

- 1 attention deficit disorder/ or attention deficit disorder with hyperactivity/ (18525)
- 2 minimal brain d?sfuction*.tw,sh. (583)
- 3 (attention deficit* or adhd).ti. (13588)
- 4 addh.tw. (130)
- 5 or/1-4 (19200)
- 6 Conduct Disorder/ (3387)
- 7 aggressive behavior/ (20528)
- 8 impulsiveness/ (5866)
- 9 exp impulse control disorders/ (704)
- 10 oppositional defiant disorder/ (1180)
- 11 distractability/ (0)
- 12 attention span/ (566)
- 13 hyperkinesis/ (7335)
- 14 inattent*.tw. (5493)
- 15 (disruptive adj4 disorder?).tw. (1722)
- 16 or/6-15 (42614)

- 17 *limit 16 to childhood (16818)*
- 18 *exp *behavior problems/ or *behavior disorders/ (25561)*
- 19 *(attention deficit* or adhd).tw. (24665)*
- 20 *18 and 19 (1215)*
- 21 *exp "side effects (treatment)"/ (45901)*
- 22 *(side effect? or adverse or harm?).tw. (75345)*
- 23 *or/21-22 (107499)*
- 24 *19 and 23 (1902)*
- 25 *5 or 20 (19683)*
- 26 *limit 25 to yr="1997 -Current" (16121)*
- 27 *17 or 24 or 26 (29952)*
- 28 *limit 27 to human (29166)*
- 29 *limit 28 to english language (27105)*
- 30 *limit 29 to (chapter or "column/opinion" or "comment/reply" or editorial or letter or reviewbook) (3829)*
- 31 *29 not 30 (23276)*
- Journal Limits
- 32 *"journal of child and adolescent psychopharmacology".jn. (1345)*
- 33 *31 and 32 (417)*
- Date Limits
- 34 *limit 33 to yr="2010 -Current" (116)*

Appendix D. Inclusion and Exclusion Criteria from Original Systematic Review

Our inclusion/exclusion criteria were developed in consultation with the Technical Expert Panel (TEP). Criteria are summarized below.

Category	Criteria
Target Population	
KQ1	The population includes children less than 6 years of age with a diagnosis of ADHD or DBD (including ODD and CD) by Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. In addition, samples where children showed clinically significant symptoms were included, defined by referral to treatment or high scores on screening measures.
KQ2	The population includes subjects of greater or equal to age 6 years who have been treated for ADHD or are a control group of ADHD subjects, diagnosed with ADHD by DSM or ICD criteria.
KQ3	The population includes subjects of any age who have been diagnosed with ADHD or treated for ADHD. Because much of this data would come from cross-sectional, survey, and medical databases using drug treatments and survey symptom checklists to identify ADHD subjects, subjects did not require a DSM or ICD diagnosis for inclusion.
Sample Size	There are no restrictions for study sample size.
Study Design and Publication Types: Inclusion	Full text reports of clinical trials and comparative observational studies were included for KQ1 and KQ2. For KQ3, we also included cross-sectional reports. Eligible designs include: <ul style="list-style-type: none">• Experimental studies with comparator groups (randomized and quasi-randomized trials)• Open label extensions following randomized controlled trials (RCTs)• Observational studies with comparator groups (retrospective and prospective cohort, and case control)

-
- For KQ3 only, noncomparative cross-sectional studies

Study Design and Publication Types: Letters, editorials, commentaries, reviews, meta-analysis, abstracts, proceedings, case reports, case series,
Exclusion qualitative studies, and these were excluded.

Non-English publications were excluded for this review.

**Note: Original inclusion/exclusion criteria extracted from Effective Health Care Program, CER #44, Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment, p. ES-4*

Appendix E. Literature Search Results (200 Randomly Selected Articles)

- Adamo N, Huo L, Adelsberg S, et al. Response time intra-subject variability: commonalities between children with autism spectrum disorders and children with ADHD. *European Child & Adolescent Psychiatry*. 23(2):69-79, 2014 Feb.
- Adler LA, Dirks B, Deas PF, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*. 74(7):694-702, 2013 Jul.
- Adler LA, Shaw DM, Spencer TJ, et al. Preliminary examination of the reliability and concurrent validity of the attention-deficit/hyperactivity disorder self-report scale v1.1 symptom checklist to rate symptoms of attention-deficit/hyperactivity disorder in adolescents. *Journal of Child & Adolescent Psychopharmacology*. 22(3):238-44, 2012 Jun.
- Arcieri R, Germinario EA, Bonati M, et al. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. *Journal of Child and Adolescent Psychopharmacology*. Vol.22(6), Dec 2012, pp. 423-431.
- Armstrong FD, Elkin TD, Brown RC, et al. Developmental function in toddlers with sickle cell anemia. *Pediatrics*. 131(2):e406-14, 2013 Feb.
- Armstrong RB, Damaraju CV, Ascher S, et al. Time course of treatment effect of OROS methylphenidate in children with ADHD. *Journal of Attention Disorders*. 16(8):697-705, 2012 Nov.
- Arnett AB, Pennington BF, Willcutt E, et al. A cross-lagged model of the development of ADHD inattention symptoms and rapid naming speed. *Journal of Abnormal Child Psychology*. 40(8):1313-26, 2012 Nov.
- Arnold LE. Introduction: EEG brain waves: a wave of the future or past? *Journal of Attention Disorders*. 17(5):371-3, 2013 Jul.
- Arns M, Conners CK, Kraemer HC, et al. A decade of EEG Theta/Beta Ratio Research in ADHD: a meta-analysis. *Journal of Attention Disorders*. 17(5):374-83, 2013 Jul.
- Babinski DE, Sibley MH, Ross JM, et al. The effects of single versus mixed gender treatment for adolescent girls with ADHD. *Journal of Clinical Child & Adolescent Psychology*. 42(2):243-250, 2013.
- Bada HS, Bann CM, Whitaker TM, et al. Protective factors can mitigate behavior problems after prenatal cocaine and other drug exposures.[Erratum appears in *Pediatrics*. 2013 Jul;132(1):175]. *Pediatrics*. 130(6):e1479-88, 2012 Dec.
- Bain EE, Apostol G, Sangal RB, et al. A randomized pilot study of the efficacy and safety of ABT-089, a novel alpha4beta2 neuronal nicotinic receptor agonist, in adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry*. 73(6):783-9, 2012 Jun.
- Banaschewski T, Jennen-Steinmetz C, Brandeis D, et al. Neuropsychological correlates of emotional lability in children with ADHD. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 53(11):1139-48, 2012 Nov.

- Barbaresi WJ, Colligan RC, Weaver AL, et al. Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study. *Pediatrics*. 131(4):637-44, 2013 Apr.
- Barker ED, Salekin RT. Irritable oppositional defiance and callous unemotional traits: is the association partially explained by peer victimization? *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 53(11):1167-75, 2012 Nov.
- Barkley RA. Distinguishing sluggish cognitive tempo from ADHD in children and adolescents: executive functioning, impairment, and comorbidity. *Journal of Clinical Child & Adolescent Psychology*. 42(2): 161-173, 2013.
- Barnard-Brak L, Schmidt M, Sulak T, et al. ADHD medication vacations and parent-child interactions by gender. *Journal of Attention Disorders*. 17(6):506-9, 2013 Aug.
- Basten MM, Althoff RR, Tiemeier H, et al. The dysregulation profile in young children: empirically defined classes in the Generation R study. *Journal of the American Academy of Child & Adolescent Psychiatry*. 52(8):841-850.e2, 2013 Aug.
- Bauermeister HH, Barkley RA, Bauermeister JA. Validity of the sluggish cognitive tempo, inattention, and hyperactivity symptom dimensions: neuropsychological and psychosocial correlates. *Journal of Abnormal Child Psychology*. 40(5):683-97, 2012 Jul.
- Becker SP, Langberg JM. Sluggish cognitive tempo among young adolescents with ADHD: relations to mental health, academic, and social functioning. *Journal of Attention Disorders*. 17(8):681-9, 2013 Nov.
- Beezhold BL, Johnston CS, Nochtka KA. Sodium benzoate-rich beverage consumption is associated with increased reporting of ADHD symptoms in college students: a pilot investigation. *Journal of Attention Disorders*. 18(3):236-41, 2014 Apr.
- Belden AC, Gaffrey MS, Luby JL. Relational aggression in children with preschool-onset psychiatric disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 51(9):889-901, 2012 Sep.
- Biederman J, Petty CR, Fried R, et al. Is the diagnosis of ADHD influenced by time of entry to school? An examination of clinical, familial, and functional correlates in children at early and late entry points. *Journal of Attention Disorders*. 18(3):179-85, 2014 Apr.
- Biederman J, Petty CR, Woodworth KY, et al. Adult outcome of attention-deficit/hyperactivity disorder: a controlled 16-year follow-up study. *Journal of Clinical Psychiatry*. 73(7):941-50, 2012 Jul.
- Bilodeau M, Simon T, Beauchamp MH, et al. Duloxetine in adults with ADHD: a randomized, placebo-controlled pilot study. *Journal of Attention Disorders*. 18(2):169-75, 2014 Feb.
- Bolden J, Rapport MD, Raiker JS, et al. Understanding phonological memory deficits in boys with attention-deficit/hyperactivity disorder (ADHD): dissociation of short-term storage and articulatory rehearsal processes. *Journal of Abnormal Child Psychology*. 40(6):999-1011, 2012 Aug.
- Bond C, Woods K, Humphrey N, et al. Practitioner Review: The effectiveness of solution focused brief therapy with children and families: a systematic and critical evaluation of the literature from 1990-2010. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 54(7):707-23, 2013 Jul.

- Bons D, van den Broek E, Scheepers F, et al. Motor, emotional, and cognitive empathy in children and adolescents with autism spectrum disorder and conduct disorder. *Journal of Abnormal Child Psychology*. 41(3):425-43, 2013 Apr.
- Bonuck K, Rao T, Xu L. Pediatric sleep disorders and special educational need at 8 years: a population-based cohort study. *Pediatrics*. 130(4):634-42, 2012 Oct.
- Bornstein MH, Hahn CS, Wolke D. Systems and cascades in cognitive development and academic achievement. *Child Development*. 84(1):154-62, 2013 Jan-Feb.
- Brammer WA, Lee SS. Prosociality and negative emotionality mediate the association of serotonin transporter genotype with childhood ADHD and ODD. *Journal of Clinical Child & Adolescent Psychology*. 42(6): 809-819, 2013.
- Brook JS, Brook DW, Zhang C. Adolescent ADHD and adult physical and mental health, work performance, and financial stress. *Pediatrics*. 131(1):5-13, 2013 Jan.
- Brown NM, Green JC, Desai MM. Need and unmet need for care coordination among children with mental health conditions. *Pediatrics*. 133(3):e530-7, 2014 Mar.
- Bugental DB, Corpuz R, Schwartz A. Preventing children's aggression: outcomes of an early intervention. *Developmental Psychology*. 48(5):1443-9, 2012 Sep.
- Bunte TL, Laschen S, Schoemaker, K, et al. Clinical usefulness of observational assessment in the diagnosis of DBD and ADHD in preschoolers. *Journal of Clinical Child & Adolescent Psychology*. 42(6): 749-761, 2013.
- Burke JD. An affective dimension within oppositional defiant disorder symptoms among boys: personality and psychopathology outcomes into early adulthood. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 53(11):1176-83, 2012 Nov.
- Burlison JD, Dwyer WO. Risk screening for ADHD in a college population: is there a relationship with academic performance? *Journal of Attention Disorders*. 17(1):58-63, 2013 Jan.
- Carelli MG, Wiberg B. Time out of mind: temporal perspective in adults with ADHD. *Journal of Attention Disorders*. 16(6):460-6, 2012 Aug.
- Chai G, Governale L, McMahon AW, et al. Trends of outpatient prescription drug utilization in US children, 2002-2010. *Pediatrics*. 130(1):23-31, 2012 Jul.
- Chen MH, Su TP, Chen YS. Attention deficit hyperactivity disorder, tic disorder, and allergy: is there a link? A nationwide population-based study. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 54(5):545-51, 2013 May.
- Chiasson JP, Stavro K, Rizkallah E, et al. Questioning the specificity of ASRS-v1.1 to accurately detect ADHD in substance abusing populations. *Journal of Attention Disorders*. 16(8):661-3, 2012 Nov.
- Chou PH, Lin CC, Lin CH, et al. Prevalence of allergic rhinitis in patients with attention-deficit/hyperactivity disorder: a population-based study. *European Child & Adolescent Psychiatry*. 22(5):301-7, 2013 May.
- Choudhry Z, Sengupta SM, Grizenko N, et al. LPHN3 and attention-deficit/hyperactivity disorder: interaction with maternal stress during pregnancy. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 53(8):892-902, 2012 Aug.
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- Coletti DJ, Pappadopulos E, Katsiotas NJ, et al. Parent perspectives on the decision to initiate medication treatment of attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*. Vol.22(3), Jun 2012, pp. 226-237.
- Colins OF, Boonmann C, Vennstra J, et al. Mental health problems and recidivism among detained male adolescents from various ethnic origins. *European Child & Adolescent Psychiatry*. 22(8):481-90, 2013 Aug.
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- Cross-Disorder Group of the Psychiatric Genomics Consortium, Genetic Risk Outcome of Psychosis (GROUP) Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis.[Erratum appears in *Lancet*. 2013 Apr 20;381(9875):1360]. *Lancet*. 381(9875):1371-9, 2013 Apr 20.
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- Dougherty LR, Tolep MR, Smith VC, et al. Early exposure to parental depression and parenting: associations with young offspring's stress physiology and oppositional behavior. *Journal of Abnormal Child Psychology*. 41(8):1299-310, 2013 Nov.
- Ellis LC, Berg-Nielsen TS, Lydersen S, et al. Smoking during pregnancy and psychiatric disorders in preschoolers. *European Child & Adolescent Psychiatry*. 21(11):635-44, 2012 Nov.
- Ercan ES, Ardic UA, Kutlu A, et al. No beneficial effects of adding parent training to methylphenidate treatment for ADHD + ODD/CD children: a 1-year prospective follow-up study. *Journal of Attention Disorders*. 18(2):145-57, 2014 Feb.

- Ezpeleta L, Granero R, de la Osa N, et al. Dimensions of oppositional defiant disorder in 3-year-old preschoolers. *Journal of Child Psychology & Psychiatry & Allied Disciplines*. 53(11):1128-38, 2012 Nov.
- Fergusson DM, Boden JM, Horwood LJ. Nine-year follow-up of a home-visitation program: a randomized trial. *Pediatrics*. 131(2):297-303, 2013 Feb.
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- Gadow KD, Drabick DA. Anger and irritability symptoms among youth with ODD: cross-informant versus source-exclusive syndromes. *Journal of Abnormal Child Psychology*. 40(7):1073-85, 2012 Oct.
- Garbutt JM, Leege E, Sterkel R, et al. Providing depression care in the medical home: what can we learn from attention-deficit/ hyperactivity disorder? *Archives of Pediatrics & Adolescent Medicine*. 166(7):672-3, 2012 Jul 1.
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Appendix F. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

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

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: Among children younger than 6 years of age with ADHD or DBD, what are the effectiveness and adverse event outcomes following treatment?			
Parent Behavior Training (PBT) – 28 studies total, 8 ADHD symptom specific (SOE high): PBT is effective in reducing both DBD and ADHD symptoms specifically (parent rated), as well as improvements in parent rated parenting strategies and sense of competence, and that benefits are maintained for several years. No long term study (12+ months) included untreated comparison groups. No difference was found between self-directed, group, and individual interventions.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
	Please explain:	New Evidence:	Please explain:
Psychostimulants (primarily immediately release MPH) – 15 studies (SOE: low):	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>Studies (primarily with mid-SES males) suggest safety and effectiveness; however, the evidence comes primarily from short-term trials lasting days to weeks with small samples and one good quality study (The Preschool ADHD Treatment Study; PATS). Results suggest a decrease in effectiveness with three or more comorbid conditions and/or psychosocial adversity. Adverse events were noted within recommended dosing levels.</p>	<p>Please explain:</p>	<p>New Evidence:</p>	<p>Please explain:</p>
<p>Key Question 2. Among people 6 years of age or older with ADHD, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of follow-up or treatment, including, but not limited to, 12 months or more of continuous treatment?</p>			
<p>Pharmacologic Agents – 18 studies</p>			
<p>Long-term psychostimulants – 12 studies (SOE: low): More research needed to make direct comparisons of long term outcomes. Concerns related the exacerbation of tics appear unfounded (though small ns). Use of psychostimulants slows the rate of growth, and increases blood pressure and heart rate to a small degree. At a group level, mean changes are clinically insignificant, although on rare occasions individuals discontinue an agent because of changes in vital signs.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
	<p>Please explain:</p>	<p>New Evidence:</p>	<p>Please explain:</p>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>Atomoxetine (ATX) - 4 studies (SOE: low): Four studies provided evidence that is both safe and effective for ADHD symptoms over 12-18 months among children and for up to three years in adults. As with psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases.</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Please explain:</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>New Evidence:</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Please explain:</p>
<p>Guanfacine Extended Release (GXR) 2 studies, only 1 GXR alone (SOE: insufficient)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Please explain:</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>New Evidence:</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Please explain:</p>
<p>Psychosocial and Behavioral Interventions, Alone and in Combination With Medication</p>			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Combined behavioral/psychosocial and medication interventions - 26 studies with 24 based on 2 cohorts (SOE: low): Studies indicate that in boys 7-9 years old with normal intelligence, both medication and combined medication/behavioral treatment are more effective in treating ADHD and ODD symptoms than psychosocial or behavioral interventions alone, particularly during the first two years	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
	Please explain:	New Evidence:	Please explain:
Behavioral/psychosocial treatment alone – 1 study (SOE: insufficient)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
	Please explain:	New Evidence:	Please explain:
Long-term academic outcomes – 13 studies (SOE: insufficient)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
	Please explain:	New Evidence:	Please explain:
Longer Term Outcomes			
Behavioral/psychosocial vs. medication plus behavioral/psychosocial	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

Archived: This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?		Do Not Know
interventions (SOE: insufficient)	Please explain:	New Evidence:		Please explain:
Psychostimulants – 15 studies (SOE: insufficient)	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
	Please explain:	New Evidence:		Please explain:
Key Question 3. How do (a) underlying prevalence of ADHD and (b) rates of diagnosis (clinical identification) and treatment for ADHD vary by geography, time period, provider type, and sociodemographic characteristics?				
Prevalence:	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>• Geography (SOE: not found): One worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger is 5.29 percent (95% CI, 5.01 to 5.56), although the percentage use of stimulants in the United States in selected subsets (e.g., Medicaid recipients) exceeds this rate. Little geographic variability was noted once methodological variability was taken into account.</p> <p>• Sex & Age (SOE: not found): Most studies show a higher prevalence in boys than girls, and children in the age group 5–10 years show the highest prevalence, though not all. Research detailing prevalence in other age groups worldwide is generally lacking, with few studies examining prevalence among preschoolers, adolescents, or adults.</p>	Please explain:	New Evidence:	Please explain:
<p>Clinical Identification:</p> <p>• Provider (SOE: not found): Providers vary in level of expertise in diagnosis of</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>ADHD, as well as in familiarity with screening instruments and classification systems. Appreciation of the combined neurodevelopmental and environmental etiologies and magnitude of impairment due to the condition has increased over the past 4 decades.</p> <ul style="list-style-type: none"> • Location (SOE: not found): Rates of diagnosis vary considerably due to cultural context, access to health care services, and provider type. Significant regional variations are noted within the United States. Reported average of 7.8%, with variability from 5.0% in Colorado to 11.1% in Alabama. In special populations (e.g. incarcerated) rates as high as 25.5% • Informant (SOE: not found): Parent and teacher observations accepted by some researchers in population studies in lieu of clinician diagnosis. Rates of diagnosis vary considerably due to cultural context. Some ethnicities are more likely to seek help or accept the diagnosis than others • Sex & Race (SOE: not found): Boys are identified as having ADHD more frequently than girls, with lower rates of diagnosis in African-American children, Hispanic children, and those living with their 	<p>Please explain:</p>	<p>New Evidence:</p>	<p>Please explain:</p>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>biological father.</p> <ul style="list-style-type: none"> • Age (SOE: not found): Primary school-age children are identified as having ADHD more frequently than older children. Formerly thought to disappear in adulthood, it is now recognized that ADHD may persist throughout the lifespan. 			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<p>Treatment:</p> <ul style="list-style-type: none"> • Location (SOE: not found): Rates of treatment vary considerably due to location and access to providers of health care services, internationally as well as regionally or even within the same community, dependent on provider type and availability, provider remuneration, and insurance status of patient. Children living in the Midwest and the South and those living in urban areas are more likely to receive medication treatment. • Provider (SOE: not found): Family practitioners in many jurisdictions, particularly those with limited access to specialists, report significant pressure from parents and teachers to prescribe stimulant medications. 	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
<ul style="list-style-type: none"> • Informant (SOE: not found): The sociocultural experience of the parent or teacher informant may influence interpretation and reporting of behaviors, willingness and persistence in seeking professional help, and/or the acceptance of treatment. Accuracy and completeness of data influence prevalence estimates, as health insurance and prescription administrative databases suggest greater increase in treatment with medications over time than repeated community surveys. • Time (SOE: not found): The rate of psychostimulant medication has increased over the past 3 decades. More recent statistics from the International Narcotics Control Board, using a denominator of standardized defined daily doses, reports that medical use of MPH (i.e., Ritalin) in the United States has increased from 7.14 S-DDDs per 1,000 inhabitants per day in 2004 to 12.03 S-DDDs per 1,000 inhabitants per day in 2008. • SES (SOE: not found): Children of lower SES are identified as having ADHD more often than children of higher SES; however, the latter are more likely to receive stimulant medications. Lower SES and minority ethnicity are associated with shorter duration of medication use. Insurance status may influence access to specialist providers in the United States. • Sex (SOE: not found): Only sparse comparative data are available examining 	<p>Please explain:</p>	<p>Please explain:</p>	<p>Please explain:</p>

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Abstracts from Relevant Literature Provided to Peer Reviewers

Adler LA, et al. 2011.

Performance improvement CME: adult ADHD. Journal of Clinical Psychiatry.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders and is now understood to be a lifelong condition for most individuals. Unfortunately, many adults with ADHD are not being diagnosed, possibly due to insufficient diagnostic criteria, the complex presentation of the disorder, and a reluctance by physicians to diagnose the disorder in adults. Additionally, many of those who have been diagnosed with ADHD do not receive adequate treatment despite the availability of established and effective agents. Performance Improvement CME (PI CME) is an educational activity in which clinicians retrospectively assess their current clinical practice, choose areas for improvement and implement interventions based on treatment guidelines and health care standards, and then re-evaluate their clinical practice to assess the improvements made. This PI CME activity focuses on improving the diagnosis and treatment of adult ADHD. Copyright 2011 Physicians Postgraduate Press, Inc.



Arcieri R, et al. Italian Attention-Deficit/Hyperactivity Disorder Regional Reference Centers. 2012.

Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. Journal of Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to assess the cardiovascular effects of drugs used for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents treated in community care centers in Italy. METHODS: This study was an open, prospective, observational study of youth with ADHD treated with atomoxetine (ATX) and methylphenidate (MPH). Measurements of blood pressure and heart rate, and electrocardiogram (ECG) assessment were performed at baseline and at regular intervals up to 24 months. RESULTS: By June 2010, 1758 youth were enrolled in the Italian ADHD National Registry. Statistically significant increases were observed in cardiovascular measures: in the MPH group after 6 months in heart rate (+2.01, $p = 0.01$); in the ATX group after 6 months in diastolic pressure (+1.60, $p = 0.01$) and in heart rate (+2.93, $p = 0.001$), and after 12 months in heart rate (+3.26, $p = 0.003$). Compared with the baseline, 59 patients had an alteration of ECG during the follow-up period. Although at 12 months, the probability of detecting an abnormal ECG was higher in the MPH group than in the ATX group, only 2 out of 30 cases at 6 months with altered ECG were considered to have experienced serious adverse events. One case was treated with ATX and one with MPH, and arrhythmia was the detected abnormality. CONCLUSIONS: Treatment with MPH and ATX in youth appears to have a small but significant impact on the cardiovascular system. The long-term impact of these medications is unknown. Several clinically meaningless ECG alterations were observed mostly in MPH-treated youth. We therefore suggest evaluating cardiovascular risks at baseline.

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Barnard-Brak L, et al. 2011.

Pharmacotherapy and academic achievement among children with attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology.

This study examined the association of pharmacological treatments and academic achievement among children with attention-deficit/hyperactivity disorder (ADHD). Results examining the association of pharmacological treatments and academic achievement among children with ADHD are mixed. Our objective was to examine this association using structural equation modeling (SEM) techniques, which may be considered more sophisticated and advanced over traditional regression techniques. To achieve the purpose, we employed a sample of children with ADHD derived from the Early Childhood Longitudinal Study-Kindergarten (ECLS-K) data. The ECLS-K provides a large, community-based, nationally representative sample of children to examine across time with respect to academic achievement outcomes. The present study reveals a statistically

nonsignificant association between pharmacological treatment and academic achievement among children with ADHD. These results derived from a large, community-based, nationally representative sample, using SEM techniques, may be considered highly generalizable.

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Bauermeister JJ, et al. 2011.

Short-term persistence of DSM-IV ADHD diagnoses: influence of context, age, and gender. Journal of the American Academy of Child & Adolescent Psychiatry.

OBJECTIVE: Little is known about the effect of social context and gender on persistence of attention-deficit/hyperactivity disorder (ADHD) in children of early and middle school years. The study compared persistence of DSM-IV ADHD and ADHD not otherwise specified (NOS) over 2 years in two groups of Puerto Rican children. METHOD: A three-wave study obtained data on Puerto Rican children 5 through 13 years of age at baseline. Samples were drawn in the South Bronx in New York (n = 1,138) and two metropolitan areas in Puerto Rico (n = 1,353). The Diagnostic Interview Schedule for Children Version IV was used to diagnose ADHD and ADHD-NOS. RESULTS: ADHD or ADHD-NOS diagnosis at wave 1 strongly predicted disorder at waves 2 and 3. ADHD had a significantly stronger predictive effect than ADHD-NOS consistently across site and gender. There was a significant interaction with baseline age. For those younger at baseline, the strength of the prediction of ADHD-NOS was relatively weak; for older children, the presence of ADHD-NOS at baseline predicted risk of subsequent ADHD or ADHD-NOS. CONCLUSIONS: Persistence of ADHD in children of similar ethnicity does not manifest differently across context and gender. Results suggest that age-specific symptom criteria and modification of age-of-onset criteria should be considered for the diagnosis. Copyright 2011 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

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Bejerot S, et al. 2010.

Two-year outcome of treatment with central stimulant medication in adult attention-deficit/hyperactivity disorder: a prospective study. Journal of Clinical Psychiatry.

BACKGROUND: Given that adults with ADHD continue to use stimulants for extended periods of time, studies on the long-term effectiveness and adverse events are warranted. The aims of this study were to investigate factors associated with persistence in treatment in an exploratory manner and to document side effects and reasons for discontinuation. METHOD: The current study describes the systematic follow-up of 133 psychiatric patients with DSM-IV-diagnosed ADHD treated with central stimulants at a specialized outpatient unit between January 1, 2001, and August 31, 2006. A standardized questionnaire, derived from the Targeted Attention-deficit Disorder Symptoms Rating Scale, was used in order to

measure improvement of the following target symptoms: hyperactivity, impulsivity, irritability, distractibility, structure/organization problems, inattention, and restlessness. RESULTS: Eighty percent of the patients were successfully treated with stimulants at the 6- to 9-month follow-up. Fifty percent remained in treatment after 2 years or more. Forty-five percent were treated for comorbid anxiety and/or depression during the study period. Only 15% dropped out because of lack of efficacy. The amount of clinical response over the first 6 to 9 months (but not at 6 weeks) predicted adherence to treatment at 2 years. The patients' heart rate increased from a least squares mean + SE of 70 + 2.2 to 80 + 2.1 bpm (P = .00003) while blood pressure remained unchanged at the > 2-year follow-up. Severe side effects or drug abuse were not detected in this cohort. CONCLUSIONS: The long-term treatment outcome shows that stimulants are effective in adult ADHD and side effects tend to be mild. Copyright 2010 Physicians Postgraduate Press, Inc.

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Boyle CA, et al. 2011.

Trends in the prevalence of developmental disabilities in US children, 1997-2008. Pediatrics.

OBJECTIVE: To fill gaps in crucial data needed for health and educational planning, we determined the prevalence of developmental disabilities in US children and in selected populations for a recent 12-year period. PARTICIPANTS AND METHODS: We used data on children aged 3 to 17 years from the 1997-2008 National Health Interview Surveys, which are ongoing nationally representative samples of US households. Parent-reported diagnoses of the following were included: attention deficit hyperactivity disorder; intellectual disability; cerebral palsy; autism; seizures; stuttering or stammering; moderate to profound hearing loss; blindness; learning disorders; and/or other developmental delays. RESULTS: Boys had a higher prevalence overall and for a number of select disabilities compared with girls. Hispanic children had the lowest prevalence for a number of disabilities compared with non-Hispanic white and black children. Low income and public health insurance were associated with a higher prevalence of many disabilities. Prevalence of any developmental disability increased from 12.84% to 15.04% over 12 years. Autism, attention deficit hyperactivity disorder, and other developmental delays increased, whereas hearing loss showed a significant decline. These trends were found in all of the sociodemographic subgroups, except for autism in non-Hispanic black children. CONCLUSIONS: Developmental disabilities are common and were reported in ~1 in 6 children in the United States in 2006-2008. The number of children with select developmental disabilities (autism, attention deficit hyperactivity disorder, and other developmental delays) has increased, requiring more health and education services. Additional study of the influence of risk-factor shifts, changes in acceptance, and benefits of early services is needed.

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Bufferd SJ, et al. 2012.

Psychiatric disorders in preschoolers: continuity from ages 3 to 6. American Journal of Psychiatry.

OBJECTIVE: Recent studies indicate that many preschoolers meet diagnostic criteria for psychiatric disorders. However, data on the continuity of these diagnoses are limited, particularly from studies examining a broad range of disorders in community samples. Such studies are necessary to elucidate the validity and clinical significance of psychiatric diagnoses in young children. The authors examined the continuity of specific psychiatric disorders in a large community sample of preschoolers from the preschool period (age 3) to the beginning of the school-age period (age 6). METHOD: Eligible families with a 3-year child were recruited from the community through commercial mailing lists. For 462 children, the child's primary caretaker was interviewed at baseline and again when the child was age 6, using the parent-report Preschool Age Psychiatric Assessment, a comprehensive diagnostic interview. The authors examined the continuity of DSM-IV diagnoses from ages 3 to 6. RESULTS: Three-month rates of disorders were relatively stable from age 3 to age 6. Children who met criteria for any diagnosis at age 3 were nearly five times as likely as the others to meet criteria for a diagnosis at age 6. There was significant homotypic continuity from age 3 to age 6 for anxiety, attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder, and heterotypic continuity between depression and anxiety, between anxiety and oppositional defiant disorder, and between ADHD and oppositional defiant disorder. CONCLUSIONS: These results indicate that preschool psychiatric disorders are moderately stable, with rates of disorders and patterns of homotypic and heterotypic continuity similar to those observed in samples of older children.

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Chen CY, et al.2011.

Differential effects of predictors on methylphenidate initiation and discontinuation among young people with newly diagnosed attention-deficit/hyperactivity disorder. [References]. Journal of Child and Adolescent Psychopharmacology.

Objective: Previous population-based studies have identified factors accounting for differential utilization of psychotropic medications among young patients with attention-deficit/hyperactivity disorders (ADHDs); yet, few analyses have addressed changes in such factors that can occur in the help-seeking process. The aim of this study was to examine patient- and service provider-level predictors for methylphenidate (MPH) initiation and discontinuation. Method: This cohort study included 10,153 newly diagnosed ADHD patients under 18 years of age in 2000, identified from the National Health Insurance Research Database. The risk association was estimated by time-dependent survival analyses, as indexed by hazard ratio. Results: Approximately 30% of young people received MPH treatment within the year of their ADHD diagnosis, and virtually none remained in treatment beyond 12 months. Regardless of co-morbidity status, the following were significantly associated with earlier initiation of MPH treatment: older age (e.g., adjusted hazard ratio [aHR] for age 12-17 = 4.5-7.6), lower socioeconomic status (aHR = 1.2-1.4), southern residence (aHR = 1.4-1.6), receiving the diagnosis while school was in session (aHR = 1.3-1.4), receiving the diagnosis from a physician specializing in pediatrics or psychiatry (aHR = 7.3-16.8), and receiving the diagnosis in a district hospital/clinic (aHR = 1.3-1.7). However, once treatment started, older ages appeared to increase the risk of early discontinuation by 15%, and the corresponding estimates for receiving initial

MPH in a regional hospital or district hospital/clinic were 27% and 32%, respectively. Change in treatment location upon subsequent visit was associated with a 58% reduction in early discontinuation. Conclusions: This information about time-varying predictors for MPH utilization throughout treatment may provide insight into the delivery of pediatric mental health services and has important implications for the design of clinical treatment programs. (PsycINFO Database Record (c) 2012 APA, all rights reserved) (journal abstract).

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Co JP, et al. 2010.

Electronic health record decision support and quality of care for children with ADHD. Pediatrics.

OBJECTIVES: The objective of this study was to assess the effect of electronic health record (EHR) decision support on physician management and documentation of care for children with attention-deficit/hyperactivity disorder (ADHD). METHODS: This study involved 79 general pediatricians in 12 pediatric primary care practices that use the same EHR who were caring for 412 children who were aged 5 to 18 years and had a previous diagnosis of ADHD. We conducted a cluster randomized trial of EHR-based decision support that included (1) clinician reminders to assess ADHD symptoms every 3 to 6 months and (2) an ADHD note template with structured fields for symptoms, treatment effectiveness, and adverse effects. The main outcome measures were (1) proportion of children with visits during the 6-month study period in which ADHD was assessed and (2) quality of documentation of ADHD assessment. Generalized estimating equations were used to control for the clustering by providers. RESULTS: Children at intervention sites were more likely to have had a visit during the study period in which their ADHD was assessed. The ADHD template was used at 32% of visits at which patients were scheduled specifically for ADHD assessment, and its use was associated with improved documentation of symptoms, treatment effectiveness, and treatment adverse effects. CONCLUSIONS: EHR-based decision support improved the likelihood that children with ADHD had visits for as well as care related to managing this condition. Better understanding of how to optimize provider use of the decision support and templates could promote additional improvements in care.

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Conduct Problems Prevention Research Group. 2011.

The effects of the fast track preventive intervention on the development of conduct disorder across childhood. Child Development.

The impact of the Fast Track intervention on externalizing disorders across childhood was examined. Eight hundred-ninety-one early-starting children (69% male; 51% African American) were randomly assigned by matched sets of schools to intervention or control conditions. The 10-year intervention addressed parent behavior-management, child social cognitive skills, reading, home visiting, mentoring, and classroom curricula. Outcomes included psychiatric diagnoses after grades 3, 6, 9, and 12 for conduct disorder, oppositional defiant disorder, attention deficit

hyperactivity disorder, and any externalizing disorder. Significant interaction effects between intervention and initial risk level indicated that intervention prevented the lifetime prevalence of all diagnoses, but only among those at highest initial risk, suggesting that targeted intervention can prevent externalizing disorders to promote the raising of healthy children. 2011 The Authors. Child Development 2011 Society for Research in Child Development, Inc.

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Connor DF, et al. 2012.

Comorbid symptom severity in attention-deficit/hyperactivity disorder: a clinical study. Journal of Clinical Psychiatry.

OBJECTIVE: Although current attention-deficit/hyperactivity disorder (ADHD) diagnostic criteria do not include emotional symptoms, externalizing behavior problems, or aggression, the practicing clinician is often faced with the evaluation and management of these symptoms when assessing and treating patients with ADHD. While much research has focused on comorbid disorders in ADHD, less attention has been directed to comorbid symptoms that may or may not meet syndrome criteria but that influence ADHD treatment planning and outcome. The aim of this study is to describe emotional and behavioral symptoms in children and adolescents with ADHD and compare them with non-ADHD control groups. METHOD: From 1995 to 2005, clinically referred children and adolescents with the combined subtype of ADHD (n = 175) or the inattentive subtype of ADHD (n = 70) as diagnosed by the primary physician (using DSM-IV criteria) were compared with a non-ADHD psychiatric control group (n = 65) and a non-ADHD community control group (n = 72) on measures that assessed emotional symptoms, externalizing behavior problems, and aggression; comparisons were controlled for age, sex, and family income. RESULTS: Both ADHD groups had depressive symptom severity equal to a non-ADHD psychiatric control group and greater than community control groups. Externalizing behavior problems and aggression were more severe in the ADHD combined subtype group compared with other groups. As ADHD symptom severity increased, externalizing behavior problems and aggression, but not internalizing symptoms, also increased in severity. Family income had an independent relationship with externalizing disorders. CONCLUSIONS: High rates of internalizing emotional symptoms, externalizing problem behaviors, and aggression were found in a clinical ADHD sample. Externalizing behavior problems and aggression appeared to be related to the hyperactive-impulsive ADHD symptom domain and to overall ADHD symptom severity. It remains an empirical question as to whether effective treatment of the core symptoms of ADHD will also reduce the presence of associated emotional and behavioral symptoms and improve daily functioning in children and adolescents with ADHD. Copyright 2012 Physicians Postgraduate Press, Inc.

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Ercan ES, et al. 2014.

No beneficial effects of adding parent training to methylphenidate treatment for ADHD + ODD/CD children: a 1-year prospective follow-up study. Journal of Attention Disorders.

OBJECTIVE: The aim of this study was to compare the effect of methylphenidate (MPH) versus MPH + parent training in children with ADHD and oppositional defiant disorder/conduct disorder (ODD/CD) over a 12-month period. METHOD: After careful screening, 120 children diagnosed with ADHD + ODD/CD were included in the study. Treatment consisted of ongoing medication management for 12 months, with or without participation in a parent-training program beginning after the 1st month. Participants were not randomly assigned to treatment groups because of ethical, practical, and methodological reasons. RESULTS: Data analyses revealed that mother-child relationship improvements and symptom severity did not benefit from parent training. CONCLUSION: The results of this study highlighted the positive role of MPH in ADHD. No significant effects were observed after the addition of parent training to MPH treatment. Clinicians should carefully follow patients' improvements and titrate the MPH dosage during long-term treatment.

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Falissard B, et al. 2010.

Short-term effectiveness of medication and psychosocial intervention in a cohort of newly diagnosed patients with inattention, impulsivity, and hyperactivity problems. Journal of Attention Disorders.

OBJECTIVE: The article discusses the ADHD Observational Research in Europe (ADORE) study that examined the impact of early treatment choices on outcome within the first few months, in previously untreated children with impairing inattention, impulsivity, and hyperactivity. METHODS: Data are collected from a longitudinal, observational study conducted in 10 European countries that involve 1,478 children (aged 6 to 18 years) with symptoms of hyperactivity, impulsivity, or inattentiveness. Linear model with a propensity score adjustment compares the decrease in ADHD-RS scores between baseline and last recorded visit across treatment groups (2 to 5 months). RESULTS: At baseline, 49.9% of participants are prescribed pharmacotherapy and 44.3% a psychosocial intervention. Analysis of the effect of treatment on the evolution of ADHD-RS scores shows a positive effect of medications and either an insignificant or negative effect of psychosocial intervention. CONCLUSIONS: Early use of medication effectively reduces ADHD symptoms in routine clinical practice in Europe. The effect of psychosocial intervention has to be interpreted cautiously because the number, length, and level of standard of the sessions are not taken into account in the analyses.

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Faraone SV, et al. 2012.

Examining the comorbidity between attention deficit hyperactivity disorder and bipolar I disorder: a meta-analysis of family genetic studies. American Journal of Psychiatry.

OBJECTIVE: The existence of comorbidity between attention deficit hyperactivity disorder (ADHD) and bipolar I disorder has been documented in clinical and epidemiological studies, in studies of children and adults, and in diagnosed ADHD and bipolar I patient samples. Yet questions remain about the validity of diagnosing bipolar I disorder in ADHD youth. The authors aim to clarify these issues by reviewing family genetic studies of ADHD and bipolar I disorder. **METHOD:** The authors applied random-effects meta-analysis to family genetic studies of ADHD and bipolar I disorder. Twenty bipolar proband studies provided 37 estimates of the prevalence of ADHD in 4,301 relatives of bipolar probands and 1,937 relatives of comparison probands. Seven ADHD proband studies provided 12 estimates of the prevalence of bipolar I disorder in 1,877 relatives of ADHD probands and 1,601 relatives of comparison probands. **RESULTS:** These studies found a significantly higher prevalence of ADHD among relatives of bipolar probands and a significantly higher prevalence of bipolar I disorder among relatives of ADHD probands. These results could not be accounted for by publication biases, unusual results from any one observation, sample characteristics, or study design features. The authors found no evidence of heterogeneity in the ADHD or bipolar family studies. **CONCLUSIONS:** The results suggest that ADHD plus bipolar comorbidity cannot be accounted for by misdiagnoses, but additional research is needed to rule out artifactual sources of comorbidity. More research is also needed to determine whether comorbidity of ADHD and bipolar I disorder constitutes a familial subtype distinct from its constituent disorders, which if confirmed would have implications for diagnostic nosology and genetic studies.

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Findling RL, et al. 2013.

A long-term open-label safety and effectiveness trial of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: Information on psychostimulant treatment in long-term studies for attention-deficit/hyperactivity disorder (ADHD) in adolescents is limited. This study aimed to assess the safety and effectiveness of lisdexamfetamine dimesylate (LDX) over 52 weeks in adolescents with ADHD.

METHODS: This open-label multicenter study enrolled eligible participants after their participation in a randomized, double-blind, placebo-controlled 4 week trial in adolescents with ADHD. Following a 4 week dose-optimization phase, participants were maintained on treatment for up to ~48 weeks on an optimal dose. Safety assessments included treatment-emergent adverse events (TEAEs), vital signs, laboratory findings, and electrocardiograms. Effectiveness measures included the ADHD Rating Scale IV (ADHD-RS-IV; primary) and Clinical Global Impressions-Improvement (CGI-I). The Youth Quality of Life-Research Version (YQOL-R) was also included in this study; raw scores are transformed to a 0-100 point scale. **RESULTS:** Of 269 enrolled (from the antecedent study), 265 (98.5%) were in the safety population and effectiveness population.

Common TEAEs (>5%) with LDX included upper respiratory tract infection (21.9%), decreased appetite (21.1%), headache (20.8%), decreased weight (16.2%), irritability (12.5%), insomnia (12.1%), nasopharyngitis (7.2%), influenza (6.8%), dizziness (5.3%), and dry mouth (5.3%). At end point, for all LDX doses in the overall safety population, mean (SD) increase from baseline in systolic blood pressure was 2.3 (10.53) mm Hg, diastolic blood pressure was 2.5 (8.37) mm Hg, and pulse rate was 6.3 (12.74) bpm. No clinically meaningful electrocardiogram or vital sign changes were observed. At end point with LDX treatment, the ADHD-RS-IV mean (SD) total score change from antecedent study baseline was -26.2 (9.75) ($p<0.001$); 87.2% of participants were improved (CGI-I=1 or 2). Baseline (antecedent study) mean (SD) YQOL-R perceptual total score was 79.8 (11.28) and increased by 3.9 (9.73) at end point ($p<0.001$). CONCLUSIONS: LDX demonstrated a long-term safety profile similar to that of other long-acting psychostimulants and was effective, as indicated by improvements in ADHD symptoms and participant-perceived YQOL, in adolescents with ADHD. CLINICAL TRIAL REGISTRATION: NCT00764868, <http://www.clinicaltrials.gov/ct2/show/NCT00764868?term=SPD489-306&rank=1>.

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Frazier TW, et al. 2011.

Prevalence and correlates of psychotropic medication use in adolescents with an autism spectrum disorder with and without caregiver-reported attention-deficit/hyperactivity disorder. Journal of Child & Adolescent Psychopharmacology.

BACKGROUND: Many youths with an autism spectrum disorder (ASD) benefit from psychotropic medication treatment of co-morbid symptom patterns consistent with attention-deficit/hyperactivity disorder (ADHD). The lack of clear indications and algorithms to direct clinical practice has led to a very poor understanding of overall medication use for these youths. The present study examined the prevalence of psychotropic medication use compared across individuals with an ASD without a caregiver-reported ADHD diagnosis (ASD-only), ADHD without ASD (ADHD-only), and an ASD with co-morbid ADHD (ASD+ADHD). Correlates of medication use were also examined. METHODS: Data on psychotropic medication from the first wave of the National Longitudinal Transition Study 2, a nationally representative study of adolescents ages 13-17 in special education, were used to compare the prevalence of medication use across the three groups, overall and by class. Separate logistic regression models were constructed for each group to examine the correlates of psychotropic medication use. Poisson regression models were used to examine correlates of the number of medications. RESULTS: Youths with ASD+ADHD had the highest rates of use (58.2%), followed by youths with ADHD-only (49.0%) and youths with ASD-only (34.3%). Youths with an ASD, both ASD-only and ASD+ADHD, used medications across a variety of medication classes, whereas stimulants were dominant among youths with ADHD-only. African American youths with ASD-only and with ASD+ADHD were less likely to receive medication than white youths, whereas race was not associated with medication use in the ADHD-only group. CONCLUSIONS: Clearer practice parameters for ADHD have likely contributed to more consistency in treatment, whereas treatment for ASD reflects a trial and error approach based on associated symptom patterns. Additional studies examining the treatment of core

and associated ASD symptoms are needed to guide pharmacologic treatment of these youths. Interventions targeting African American youths with ASD and the physicians who serve them are also warranted.

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Fusar-Poli P, et al. 2012.

Striatal dopamine transporter alterations in ADHD: pathophysiology or adaptation to psychostimulants? A meta-analysis. American Journal of Psychiatry.

BACKGROUND: Striatal dopamine transporter abnormalities are thought to underlie the pathophysiology and psychostimulant treatment of attention deficit hyperactivity disorder (ADHD). However, individual studies using single photon emission tomography (SPECT) or positron emission tomography (PET) have yielded inconsistent results, i.e., both high and low striatal dopamine transporter levels. METHOD: Nine SPECT and PET studies investigating striatal dopamine transporter density in ADHD patients (N=169) and age-, gender-, and IQ-matched healthy comparison subjects (N=173) were included in a quantitative meta-analysis. Binding potentials in the striatum and demographic, clinical, and methodological variables were extracted from each publication or obtained directly from authors. Hedges' g was used as a measure of effect size in an analysis using Comprehensive Meta-Analysis software. Publication bias was assessed with funnel plots and Egger's intercept. Heterogeneity was addressed with the Q statistic and I2 index. RESULTS: Striatal dopamine transporter density was 14% higher on average in the ADHD group than in the healthy comparison group. However, heterogeneity across studies was large and statistically significant. Meta-regression analyses showed that the percentage of subjects without exposure to psychostimulants was negatively correlated with dopamine transporter density; density was higher in patients with previous medication exposure and lower in medication-naive patients. There was no moderating effect for age, comorbidity, gender, year of publication, or imaging technique. There was no publication bias, and sensitivity analysis confirmed robustness of the results. CONCLUSIONS: Striatal dopamine transporter density in ADHD appears to depend on previous psychostimulant exposure, with lower density in drug-naive subjects and higher density in previously medicated patients.

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Garbe E, et al. 2012.

Drug treatment patterns of attention-deficit/hyperactivity disorder in children and adolescents in Germany: Results from a large population-based cohort study. [References]. Journal of Child and Adolescent Psychopharmacology.

Objective: Despite a substantial increase in total methylphenidate (MPH) prescriptions in Germany over the last 20 years, and the introduction of modified release MPH (MR MPH) and atomoxetine (ATX), remarkably little is known about treatment patterns of attention-deficit/hyperactivity disorder (ADHD) in individual patients. Methods: Usage patterns of ADHD drugs in children and adolescents in Germany were analyzed using

data from one large German health insurance including > 7,200,000 members. Of those, 6210 ADHD patients newly diagnosed in 2005 were followed for a maximum of 4 years. Kaplan-Meier estimates were calculated for onset and discontinuation of ADHD drug treatment. Predictors of time until drug treatment initiation were assessed by Cox regression. Results: During follow-up, 52.0% of ADHD subjects (53.4% of boys, 47.5% of girls) received ADHD drug treatment. The majority of them (91.6%) were started on MPH, with immediate release MPH (IR MPH) being the initial treatment choice in 75.3%. In these subjects, change to drug treatment with MR MPH in the first year occurred in 48% by switch or addition. Significant predictors of drug treatment were behavioral and emotional disorders (HR= 1.13; 95% CI 1.03-1.24) and a diagnosis of ADHD with conduct disorder (HR = 1.21, 95% CI 1.12-1.32), whereas young age showed a protective effect. After 6, 12, and 24 months of treatment initiation, 22.4%, 43.4%, and 66.3% of treated girls, and 17.8%, 36.1%, and 54.1% of treated boys had discontinued ADHD treatment. Conclusion: Drug treatment of ADHD was relatively common in Germany and more frequent in boys than in girls. IR MPH was the predominant treatment choice at treatment initiation. Approximately 20% of treated subjects discontinued drug treatment within the first 6 months, with girls stopping drug treatment earlier than boys. The reasons for early drug discontinuation need to be further explored. (PsycINFO Database Record (c) 2013 APA, all rights reserved) (journal abstract).

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Germinario EA, et al. 2013.

Attention-deficit/hyperactivity disorder drugs and growth: An Italian prospective observational study. [References]. Journal of Child and Adolescent Psychopharmacology.

OBJECTIVE: This study was conducted to assess the long-term effect of methylphenidate (MPH) or atomoxetine (ATX) on growth in attention-deficit/hyperactivity disorder (ADHD) drug-naive children. DESIGN: The study was an observational, post-marketing, fourth phase study. Methods: Data on height and weight were collected at baseline and every 6 months up to 24 months. RESULTS: Both ATX and MPH lead to decreased height gain (assessed by means of z-scores); the effect was significantly higher for ATX than for MPH. At any time, height z-score decrease in the ATX group was higher than the corresponding decrease observed in the MPH group, but the difference was significantly relevant only during the first year of treatment. An increment of average weight was observed both in patients treated with MPH and in those treated with ATX. However, using Tanner's percentile, a subset of patients showed a degree of growth lower than expected. This negative effect was significantly higher for ATX than for MPH. CONCLUSIONS: We conclude that ADHD drugs show a negative effect on linear growth in children in middle term. Such effect appears more evident for ATX than for MPH. (PsycINFO Database Record (c) 2013 APA, all rights reserved) (journal abstract).

Getahun D, et al. 2013.

In utero exposure to ischemic-hypoxic conditions and attention-deficit/hyperactivity disorder. Pediatrics.

OBJECTIVE: To examine the association between ischemic-hypoxic conditions (IHCs) and attention-deficit/hyperactivity disorder (ADHD) by gestational age and race/ethnicity. METHODS: Nested case-control study using the Kaiser Permanente Southern California (KPSC) medical records. The study cohort included children aged 5 to 11 years who were delivered and cared for in the KPSC between 1995 and 2010 (N = 308,634). Case children had a diagnosis of ADHD and received > 2 prescriptions specific to ADHD during the follow-up period. For each case, 5 control children were matched by age at diagnosis. Exposures were defined by using International Classification of Diseases, Ninth Revision codes. A conditional regression model was used to estimate adjusted odds ratios (ORs). RESULTS: Among eligible children, 13,613 (4.3%) had a diagnosis of ADHD. Compared with control children, case children were more likely to be male and of white or African American race/ethnicity. Case children were more likely to be exposed to IHCs (OR = 1.16, 95% confidence interval [CI] 1.11-1.21). When stratified by gestational age, cases born at 28 to 33, 34 to 36, and 37 to 42 weeks of gestation, were more likely to be exposed to IHCs (ORs, 1.6 [95% CI 1.2-2.1], 1.2 [95% CI 1.1-1.3], and 1.1 [95% CI 1.0-1.2], respectively) compared with controls. IHC was associated with increased odds of ADHD across all race/ethnicity groups. CONCLUSIONS: These findings suggest that IHCs, especially birth asphyxia, respiratory distress syndrome, and preeclampsia, are independently associated with ADHD. This association was strongest in preterm births.

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Gleason MM, et al. 2011.

Epidemiology of psychiatric disorders in very young children in a Romanian pediatric setting. European Child & Adolescent Psychiatry.

A growing literature demonstrates that early clinical intervention can reduce risks of adverse psychosocial outcomes. A first step necessary for developing early intervention services is to know the prevalence of clinical disorders, especially in systems that are rebuilding, such as Romania, where the mental health system was dismantled under Ceausescu. No epidemiologic studies have examined prevalence of psychiatric disorders in young children in Romania. The objective of this study was to determine the prevalence of psychiatric disorders in Romanian children 18-60 months in pediatric settings. Parents of 1,003 children 18-60 months in pediatric waiting rooms of two pediatric hospitals completed background information, the Child Behavior Checklist (CBCL). A subgroup over-sampled for high mental health problems were invited to participate in the Preschool Age Psychiatric Assessment. Rates of mental health problems were similar to the US norms on the CBCL. The weighted prevalence of psychiatric disorders in these children was 8.8%, with 5.4% with emotional disorders and 1.4% with behavioral disorders. Comorbidity occurred in nearly one-fourth of the children with a psychiatric disorder and children who met diagnostic criteria had more functional impairment than those without. Of children who met criteria for a psychiatric disorder, 10% of parents were concerned about their child's emotional or behavioral health.

This study provides prevalence rates of psychiatric disorders in young Romanian children, clinical characteristic of the children and families that can guide developing system of care. Cultural differences in parental report of emotional and behavioral problems warrant further examination.

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Goetz M, et al. 2012.

A 12-month prospective, observational study of treatment regimen and quality of life associated with ADHD in central and eastern europe and eastern Asia. Journal of Attention Disorders.

OBJECTIVES: This prospective, observational, non-randomized study aimed to describe the relationship between treatment regimen prescribed and the quality of life (QoL) of ADHD patients in countries of Central and Eastern Europe (CEE) and Eastern Asia over 12 months. **METHODS:** 977 Male and female patients aged 6-17 years seeking treatment for symptoms of ADHD were assessed using the Child and Adolescent Symptom Inventory-4 Parent Checklists, and the Clinical Global Impressions-ADHD-Severity scale. QoL was assessed using the Child Health and Illness Profile-Child Edition parent report form. Patients were grouped according to whether they were prescribed psycho- and/or pharmacotherapy (treatment) or not (no/'other' treatment). **RESULTS:** No statistically significant differences were observed between cohorts (treatment vs. no/'other' treatment) in terms of change in QoL, although there was improvement over 12 months, with a greater improvement experienced by patients in the treatment cohort in both study regions (CEE and Eastern Asia). Psychoeducation/counselling and methylphenidate were the predominant ADHD treatments prescribed. **CONCLUSIONS:** Although both treatment and no/'other' treatment cohorts showed improvements in mean QoL over 12 months, the difference was small and not statistically significant. A major limitation was the higher than anticipated number of patients switching treatments, predominantly from the no/'other' treatment cohort.

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Gunther T, et al. 2010.

Sex differences in attentional performance and their modulation by methylphenidate in children with attention-deficit/hyperactivity disorder. [References]. Journal of Child and Adolescent Psychopharmacology.

BACKGROUND: Still little is known about neuropsychological differences between boys and girls with attention-deficit/hyperactivity disorder (ADHD) and whether there are sex-specific differences in the modulation of attentional performance by methylphenidate (MPH). **METHOD:** In this study, 27 males and 27 females between 8-12 years old and with ADHD were investigated in a double-blind, placebo-controlled trial on five computerized attention tests (0.25 vs. 0.5 mg/kg MPH as a single dose, versus placebo). **RESULTS:** Boys and girls with ADHD did not differ with respect to age, intelligence quotient (IQ), symptom severity, comorbidity patterns, and ADHD subtype. However, ADHD boys were more

impulsive on a sustained attention task, whereas girls with ADHD had more deficits on tasks measuring selective attention. Attentional performance increased differentially as a function of MPH dose, with some tasks showing linear improvement with higher dosage whereas more complex tasks in particular showed inverse U-shaped patterns of MPH effects. However, these effects were comparable between girls and boys. CONCLUSIONS: Our data suggest that there are some gender differences in attentional performance in subjects with ADHD in a clinical sample, even if symptom severity and co-morbidity are controlled; however, modulation of attention by MPH does not seem to differ between sexes. (PsycINFO Database Record (c) 2012 APA, all rights reserved) (journal abstract).

Kratochvil CJ, et al. 2011.

A double-blind, placebo-controlled study of atomoxetine in young children with ADHD. Pediatrics.

OBJECTIVE: To evaluate the efficacy and tolerability of atomoxetine for the treatment of attention-deficit/hyperactivity disorder (ADHD) in 5- and 6-year-old children. METHODS: This was an 8-week, double-blind, placebo-controlled randomized clinical trial of atomoxetine in 101 children with ADHD. Atomoxetine or placebo was flexibly titrated to a maximum dose of 1.8 mg/kg per day. The pharmacotherapist reviewed psychoeducational material on ADHD and behavioral-management strategies with parents during each study visit. RESULTS: Significant mean decreases in parent ($P = .009$) and teacher ($P = .02$) ADHD-IV Rating Scale scores were demonstrated with atomoxetine compared with placebo. A total of 40% of children treated with atomoxetine met response criteria (Clinical Global Impression-Improvement Scale indicating much or very much improved) compared with 22% of children on placebo, which was not significant ($P = .1$). Decreased appetite, gastrointestinal upset, and sedation were significantly more common with atomoxetine than placebo. Although some children demonstrated a robust response to atomoxetine, for others the response was more attenuated. Sixty-two percent of subjects who received atomoxetine were moderately, markedly, or severely ill according to the Clinical Global Impression-Severity Scale at study completion. CONCLUSIONS: To our knowledge, this is the first randomized controlled trial of atomoxetine in children as young as 5 years. Atomoxetine generally was well tolerated and reduced core ADHD symptoms in the children on the basis of parent and teacher reports. Reductions in the ADHD-IV Rating Scale scores, however, did not necessarily translate to overall clinical and functional improvement, as demonstrated on the Clinical Global Impression-Severity Scale and the Clinical Global Impression-Improvement Scale. Despite benefits, the children in the atomoxetine group remained, on average, significantly impaired at the end of the study.

Larson K, et al. 2011.

Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. Pediatrics.

OBJECTIVE: To determine patterns of comorbidity, functioning, and service use for US children with attention-deficit/hyperactivity disorder (ADHD). METHODS: Bivariate and multivariable cross-sectional analyses were conducted on data from the 2007 National Survey of Children's Health on 61 779 children ages 6 to 17 years, including 5028 with ADHD. RESULTS: Parent-reported diagnosed prevalence of ADHD was 8.2%. Children with ADHD were more likely to have other mental health and neurodevelopmental conditions. Parents reported that 46% of children with ADHD had a learning disability versus 5% without ADHD, 27% vs 2% had a conduct disorder, 18% vs 2% anxiety, 14% vs 1% depression, and 12% vs 3% speech problems (all $P < .05$). Most children with ADHD had at least 1 comorbid disorder: 33% had 1, 16% had 2, and 18% had 3 or more. The risk for having 3 or more comorbidities was 3.8 times higher for poor versus affluent children (30% vs 8%). Children with ADHD had higher odds of activity restriction (odds ratio: 4.14 [95% confidence interval: 3.34-5.15]), school problems (odds ratio: 5.18 [95% confidence interval: 4.47-6.01]), grade repetition, and poor parent-child communication, whereas social competence scores were lower and parent aggravation higher. Functioning declined in a stepwise fashion with increasing numbers of comorbidities, and use of health and educational services and need for care coordination increased. CONCLUSIONS: Clinical management of ADHD must address multiple comorbid conditions and manage a range of adverse functional outcomes. Therapeutic approaches should be responsive to each child's neurodevelopmental profile, tailored to their unique social and family circumstances, and integrated with educational, mental health and social support services.

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Lecendreux M, et al. 2011.

Prevalence of attention deficit hyperactivity disorder and associated features among children in France. Journal of Attention Disorders.

BACKGROUND: Earlier studies point to the prevalence of attention deficit hyperactivity disorder (ADHD) to be similar around the world. There is, however, a wide variety in estimates. The prevalence of ADHD in youth has never been examined in France. METHOD: Starting with 18 million telephone numbers, 7,912 numbers are randomly selected. Among the 4,186 eligible families, 1,012 (24.2%) are successfully recruited. A telephone interview is administered to all families about a child in the 6 to 12 age range. It covered family living situation, school performance, symptoms of ADHD, conduct disorder (CD), and oppositional-defiant disorder (ODD), and other features of ADHD. RESULTS: The prevalence of ADHD in France is between 3.5% and 5.6%. The population prevalence of treatment for ADHD is 3.5%. ADHD youth are more likely to be men than women, and, compared to non-ADHD children, ADHD children are more likely to have CD and ODD. Having ADHD is associated with a family history of the disorder. The ADHD youth are more likely to have had learning difficulties, to have repeated a grade, and to be functioning academically below grade level. CONCLUSIONS: The epidemiology of ADHD in French children is similar to the epidemiology of ADHD in other countries. The disorder occurs in between 3.5% to 5.6% of youth and is more common among boys than among girls. The authors replicate the well-known association of ADHD with CD, ODD, and indices of school failure. The impact of ADHD symptoms on school performance highlights the importance of screening for such symptoms in schools.

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Lensing MB, et al. 2013.

Four-year outcome in psychopharmacologically treated adults with attention-deficit/hyperactivity disorder: a questionnaire survey. Journal of Clinical Psychiatry.

OBJECTIVE: In adults with attention-deficit/hyperactivity disorder (ADHD), pharmacotherapy is a recommended treatment option. However, research on long-term outcome with such treatment has been scarce. METHOD: A questionnaire survey was completed by adults with ADHD, diagnosed according to ICD-10/DSM-IV criteria and approved for pharmacotherapy during 2003 to 2005, living in southeastern Norway. The questionnaire was conducted from November 2008 to April 2009. Of an eligible number of 1,096 subjects, 1,080 remained at follow-up; 371 subjects (34.4%) agreed to participate, and 368 of these reported having ever been treated with ADHD medication. Baseline characteristics and self-reported outcome were studied by time on psychopharmacologic treatment. Primary outcome measures were the Adult ADHD Self-Report Scale version 1.1 (ASRS) Screener and the Mental Health Index-5 (MHI-5). Based on cutoff scores for these instruments, 2 groups (favorable outcome vs others) were created to study possible predictors of outcome status. RESULTS: Self-reported baseline ADHD symptoms and impairment did not differ between participants and nonparticipants. Mean observation time was 4.5 years (range, 3.5-6.0 years). At follow-up, mean age was 36.5 years. Altogether, 270 patients (73.4%) had been treated for more than 24 months. They reported better outcome on all measures compared to those treated for 24 months or less (mean values: ASRS Screener score: 12.8 vs 15.3; MHI-5 score: 63.7 vs 57.7). The favorable outcome group consisted of 79 participants (21.5%). Comorbidity at baseline predicted poorer outcome than did no comorbid illness. CONCLUSIONS: In adults with ADHD, pharmacologic treatment for more than 2 years was associated with better functioning than treatment for 2 years or less. Comorbidity at baseline predicted poorer outcome. Copyright 2013 Physicians Postgraduate Press, Inc.

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Lindemann C, et al. 2012.

Age-specific prevalence, incidence of new diagnoses, and drug treatment of attention-deficit/hyperactivity disorder in Germany. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to estimate the prevalence and incidence of new diagnoses of attention-deficit/hyperactivity disorder (ADHD) and assess drug treatment of ADHD in the 3-17 year age group in Germany. METHOD: We analysed data from the German Pharmacoepidemiological Research Database (GePaRD) for the years 2004-2006. The GePaRD includes claim records of 14,000,000 members of four statutory health insurances, representing 17% of the German population. The assessment of ADHD diagnoses was based on International Classification of Diseases version 10 (ICD-10) codes in outpatient and hospital data. RESULTS: In 2005, the age-standardized prevalence and

incidence of new diagnoses were 2.5% and 9/1000 person-years, respectively. Both measures were 3-4 times higher for males than for females. Incidence of new ADHD diagnoses increased linearly up to the age of 8 years for boys and 9 years for girls and decreased abruptly thereafter. In the calendar quarter of the initial ADHD diagnosis, 9.4% (95% confidence interval [CI] 8.9-9.8%) received methylphenidate or atomoxetine and 36.8% (95% CI 36.1-37.6%) received at least one prescription of either drug within the first year. Initiation of drug treatment and choice of drug were similar for both sexes. CONCLUSIONS: ADHD is a common condition among children and youth in Germany. There are substantial differences by sex in the prevalence and incidence of new ADHD diagnoses, but only a small difference in drug treatment among those diagnosed with ADHD. A relatively low percentage of children receives drug treatment in the first year after the initial diagnosis of ADHD.

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Lindemann C, et al. 2012.

Age-specific prevalence, incidence of new diagnoses, and drug treatment of attention-deficit/hyperactivity disorder in Germany. [References]. Journal of Child and Adolescent Psychopharmacology.

OBJECTIVE: The purpose of this study was to estimate the prevalence and incidence of new diagnoses of attention-deficit/ hyperactivity disorder (ADHD) and assess drug treatment of ADHD in the 3-17 year age group in Germany. METHOD: We analysed data from the German Pharmacoepidemiological Research Database (GePaRD) for the years 2004- 2006. The GePaRD includes claim records of 14,000,000 members of four statutory health insurances, representing 17% of the German population. The assessment of ADHD diagnoses was based on International Classification of Diseases version 10 (ICD-10) codes in outpatient and hospital data. RESULTS: In 2005, the age-standardized prevalence and incidence of new diagnoses were 2.5% and 9/1000 person-years, respectively. Both measures were 3-4 times higher for males than for females. Incidence of new ADHD diagnoses increased linearly up to the age of 8 years for boys and 9 years for girls and decreased abruptly thereafter. In the calendar quarter of the initial ADHD diagnosis, 9.4% (95% confidence interval [CI] 8.9-9.8%) received methylphenidate or atomoxetine and 36.8% (95% CI 36.1-37.6%) received at least one prescription of either drug within the first year. Initiation of drug treatment and choice of drug were similar for both sexes. CONCLUSIONS: ADHD is a common condition among children and youth in Germany. There are substantial differences by sex in the prevalence and incidence of new ADHD diagnoses, but only a small difference in drug treatment among those diagnosed with ADHD. A relatively low percentage of children receives drug treatment in the first year after the initial diagnosis of ADHD. (PsycINFO Database Record (c) 2012 APA, all rights reserved) (journal abstract).

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Lindstrom K, et al. 2011.

Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. Pediatrics.

OBJECTIVE: Previous studies have demonstrated an increased risk for attention-deficit/hyperactivity disorder (ADHD) in follow-up studies of preterm survivors from NICUs. In this study we analyzed the effect of moderate as well as extreme preterm birth on the risk for ADHD in school age, taking into account genetic, perinatal, and socioeconomic confounders. METHODS: Register study in a Swedish national cohort of 1 180 616 children born between 1987 and 2000, followed up for ADHD medication in 2006 at the age of 6 to 19 years. Logistic regression was used to test hypotheses. A within-mother-between-pregnancy design was used to estimate the importance of genetic confounding in a subpopulation of offspring (N = 34 334) of mothers who had given birth to preterm (<34 weeks) as well as term infants. RESULTS: There was a stepwise increase in odds ratios for ADHD medication with increasing degree of immaturity at birth; from 2.1 (1.4-2.7) for 23 to 28 weeks' gestation, to 1.6 (1.4-1.7) for 29 to 32 weeks', 1.4 (1.2-1.7) for 33 to 34 weeks', 1.3 (1.1-1.4) for 35 to 36 weeks', and 1.1 (1.1-1.2) for 37 to 38 weeks' gestation compared with infants born at 39 to 41 weeks' gestation in the fully adjusted model. The odds ratios for the within-mother-between-pregnancy analysis were very similar. Low maternal education increased the effect of moderate, but not extreme, preterm birth on the risk for ADHD. CONCLUSION: Preterm and early term birth increases the risk of ADHD by degree of immaturity. This main effect is not explained by genetic, perinatal, or socioeconomic confounding, but socioeconomic context modifies the risk of ADHD in moderately preterm births.

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Malone PS, et al. 2010.

A mixture-model approach to linking ADHD to adolescent onset of illicit drug use. Developmental Psychology.

Prior research findings have been mixed as to whether attention-deficit/hyperactivity disorder (ADHD) is related to illicit drug use independent of conduct problems (CP). With the current study, the authors add to this literature by investigating the association between trajectories of ADHD symptoms across childhood and adolescence and onset of illicit drug use, with and without controlling for CP. In a longitudinal panel study of a community sample of 754 girls and boys recruited in kindergarten, this research question was examined with a combination of growth mixture modeling (to model parent-reported ADHD symptom trajectories) and survival analysis (to model youth-reported initiation of illicit drug use). Results revealed a 3-class model of ADHD trajectories, with 1 class exhibiting no or minimal symptoms throughout childhood and adolescence, another class showing a convex shape (an increase, then a decrease in symptoms) across time, and a third class showing a concave shape (a decrease, then a slight increase in symptoms) over time. The concave-trajectory class demonstrated significantly earlier onset of illicit drug use than the minimal-problem class, with the convex-trajectory class falling between (but not significantly different from either of the other two classes). These results did not change when the authors added CP to the model as a covariate. Implications of findings for theory and practice are discussed.

McGrath PJ, et al. 2011.

Telephone-based mental health interventions for child disruptive behavior or anxiety disorders: randomized trials and overall analysis. Journal of the American Academy of Child & Adolescent Psychiatry.

OBJECTIVE: Most children with mental health disorders do not receive timely care because of access barriers. These initial trials aimed to determine whether distance interventions provided by nonprofessionals could significantly decrease the proportion of children diagnosed with disruptive behavior or anxiety disorders compared with usual care. METHOD: In three practical randomized controlled trials, 243 children (80 with oppositional-defiant, 72 with attention-deficit/hyperactivity, and 91 with anxiety disorders) were stratified by DSM-IV diagnoses and randomized to receive the Strongest Families intervention (treatment) or usual care (control). Assessments were blindly conducted and evaluated at 120, 240, and 365 days after randomization. The intervention consisted of evidence-based participant materials (handbooks and videos) and weekly telephone coach sessions. The main outcome was mental health diagnosis change. RESULTS: Intention-to-treat analysis showed that for each diagnosis significant treatment effects were found at 240 and 365 days after randomization. Moreover, in the overall analysis significantly more children were not diagnosed as having disruptive behavior or anxiety disorders in the treatment group than the control group (120 days: $\chi^2(1) = 13.05$, $p < .001$, odds ratio 2.58, 95% confidence interval 1.54-4.33; 240 days: $\chi^2(1) = 20.46$, $p < .001$, odds ratio 3.44, 95% confidence interval 1.99-5.92; 365 days: $\chi^2(1) = 13.94$, $p < .001$, odds ratio 2.75, 95% confidence interval 1.61-4.71). CONCLUSIONS: Compared with usual care, telephone-based treatments resulted in significant diagnosis decreases among children with disruptive behavior or anxiety. These interventions hold promise to increase access to mental health services. CLINICAL TRIAL REGISTRATION INFORMATION: Strongest Families: Pediatric Disruptive Behaviour Disorder, <http://www.clinicaltrials.gov>, NCT00267579; Strongest Families: Pediatric Attention-Deficit/Hyperactivity Disorder, <http://www.clinicaltrials.gov>, NCT00267605; and Strongest Families: Pediatric Anxiety, <http://www.clinicaltrials.gov>, NCT00267566. Copyright 2011 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

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Morgan PL, et al. 2013.

Racial and ethnic disparities in ADHD diagnosis from kindergarten to eighth grade. Pediatrics.

OBJECTIVE: Whether and to what extent racial/ethnic disparities inattention-deficit/hyperactivity disorder (ADHD) diagnosis occur across early and middle childhood is currently unknown. We examined the over-time dynamics of race/ethnic disparities in diagnosis from kindergarten to eighth grade and disparities in treatment in fifth and eighth grade. METHODS: Analyses of the nationally representative Early Childhood Longitudinal Study, Kindergarten Class of 1998-1999 (N = 17 100) using discrete-time hazard modeling. RESULTS: Minority children were less

likely than white children to receive an ADHD diagnosis. With time-invariant and -varying confounding factors statistically controlled the odds of ADHD diagnosis for African Americans, Hispanics, and children of other races/ethnicities were 69% (95% confidence interval [CI]: 60%-76%), 50% (95% CI: 34%-62%), and 46% (95% CI: 26%-61%) lower, respectively, than for whites. Factors increasing children's risk of an ADHD diagnosis included being a boy, being raised by an older mother, being raised in an English-speaking household, and engaging in externalizing problem behaviors. Factors decreasing children's risk of an ADHD diagnosis included engaging in learning-related behaviors (eg, being attentive), displaying greater academic achievement, and not having health insurance. Among children diagnosed with ADHD, racial/ethnic minorities were less likely than whites to be taking prescription medication for the disorder. CONCLUSIONS: Racial/ethnic disparities in ADHD diagnosis occur by kindergarten and continue until at least the end of eighth grade. Measured confounding factors do not explain racial/ethnic disparities in ADHD diagnosis and treatment. Culturally sensitive monitoring should be intensified to ensure that all children are appropriately screened, diagnosed, and treated for ADHD.

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Palli SR, et al. 2012.

Persistence of stimulants in children and adolescents with attention-deficit/hyperactivity disorder. [References]. Journal of Child and Adolescent Psychopharmacology.

OBJECTIVE: To examine the persistence of three newly initiated stimulant preparations among Medicaid children and adolescents with attention-deficit/hyperactivity disorder (ADHD) diagnosis. METHODS: A retrospective longitudinal claims analysis was conducted by using Medicaid analytical extract data of four states. The study focused on patients between 6 and 19 years of age with ADHD diagnosis and a stimulant prescription from January 2003 to December 2005. Stimulants were grouped into short-acting stimulants (SAS), intermediate-acting stimulants (IAS), and long-acting stimulants (LAS). Persistence was measured by totaling the number of days the patient remained on the index stimulant therapy from the index prescription date provided the refill gap between two consecutive stimulant claims was no more than 30 days. All the stimulant recipients were uniformly followed for 1 year (365 days). Survival time ratios (STR) were calculated by using accelerated failure time models to examine variation in index stimulant persistence for each stimulant class. RESULTS: Among the 46,135 patients with ADHD continuously followed for 1 year, 8,260 were SAS users, 4,314 were IAS users, and 33,561 were LAS users. Children who received IAS medications had 4% shorter persistence (STR, 0.96 [95% confidence interval [CI], 0.93-0.98]) when compared with those who received SAS medications, whereas those who received index LAS medications had 29% longer persistence (STR, 1.29 [95% CI, 1.27-1.32]). Multivariate accelerated failure time models revealed that Blacks and Hispanics had consistently lower persistence than their counterparts. Foster care was positively associated with index stimulant persistence in the three stimulant types. Further, addition of another stimulant and other psychotropic medications significantly improved persistence of index stimulant in all three stimulant classes. CONCLUSIONS: LAS had comparatively longer

persistence than other stimulants. An understanding of demographic and clinical characteristics that influence treatment continuation can help improve stimulant persistence rates in ADHD. (PsycINFO Database Record (c) 2012 APA, all rights reserved) (journal abstract).

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Pelsser LM, et al. 2011.

Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial. Lancet.

BACKGROUND: The effects of a restricted elimination diet in children with attention-deficit hyperactivity disorder (ADHD) have mainly been investigated in selected subgroups of patients. We aimed to investigate whether there is a connection between diet and behaviour in an unselected group of children. **METHODS:** The Impact of Nutrition on Children with ADHD (INCA) study was a randomised controlled trial that consisted of an open-label phase with masked measurements followed by a double-blind crossover phase. Patients in the Netherlands and Belgium were enrolled via announcements in medical health centres and through media announcements. Randomisation in both phases was individually done by random sampling. In the open-label phase (first phase), children aged 4-8 years who were diagnosed with ADHD were randomly assigned to 5 weeks of a restricted elimination diet (diet group) or to instructions for a healthy diet (control group). Thereafter, the clinical responders (those with an improvement of at least 40% on the ADHD rating scale [ARS]) from the diet group proceeded with a 4-week double-blind crossover food challenge phase (second phase), in which high-IgG or low-IgG foods (classified on the basis of every child's individual IgG blood test results) were added to the diet. During the first phase, only the assessing paediatrician was masked to group allocation. During the second phase (challenge phase), all persons involved were masked to challenge allocation. Primary endpoints were the change in ARS score between baseline and the end of the first phase (masked paediatrician) and between the end of the first phase and the second phase (double-blind), and the abbreviated Conners' scale (ACS) score (unmasked) between the same timepoints. Secondary endpoints included food-specific IgG levels at baseline related to the behaviour of the diet group responders after IgG-based food challenges. The primary analyses were intention to treat for the first phase and per protocol for the second phase. INCA is registered as an International Standard Randomised Controlled Trial, number ISRCTN 76063113.

FINDINGS: Between Nov 4, 2008, and Sept 29, 2009, 100 children were enrolled and randomly assigned to the control group (n=50) or the diet group (n=50). Between baseline and the end of the first phase, the difference between the diet group and the control group in the mean ARS total score was 237 (95% CI 186-288; p<00001) according to the masked ratings. The difference between groups in the mean ACS score between the same timepoints was 118 (95% CI 92-145; p<00001). The ARS total score increased in clinical responders after the challenge by 208 (95% CI 143-273; p<00001) and the ACS score increased by 116 (77-154; p<00001). In the challenge phase, after challenges with either high-IgG or low-IgG foods, relapse of ADHD symptoms occurred in 19 of 30 (63%) children, independent of the IgG blood levels. There were no harms or adverse events reported in both phases. **INTERPRETATION:** A strictly supervised restricted elimination diet is a valuable instrument to assess whether ADHD is induced by food. The prescription of diets on the basis of IgG blood tests should be discouraged. **FUNDING:** Foundation of Child and

Behaviour, Foundation Nuts Ohra, Foundation for Children's Welfare Stamps Netherlands, and the KF Hein Foundation. Copyright 2011 Elsevier Ltd. All rights reserved.

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Powell SG, et al. 2011.

Long-term treatment of ADHD with stimulants: a large observational study of real-life patients. Journal of Attention Disorders.

OBJECTIVE: To evaluate 410 real-life patients treated with stimulants and assessed systematically over several years. METHOD: Naturalistic observational study. A database was compiled on the basis of a review of the medical charts of patients attending a specialized ADHD clinic.

RESULTS: The diversity of ADHD patients was evident from the comorbidity, age at start, comedication, and treatment needs over time. Dosages corresponded to guidelines in most patients, but some needed higher dosages or got along on lower dosages for long periods. Age at start and comorbidity influenced dosage, and dosage was associated to differential outcome groups. CONCLUSION: The study findings underscored the diversity of ADHD patients and that individual factors should be taken into account when tailoring individual treatment schedules. Findings further showed that stimulant dosages are dynamic over time and depend on individual factors that individual factors influence outcome, and that patients with ADHD should be individually monitored and stimulant dosages adjusted continuously.

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Rajendran K, et al. 2013.

Association between variation in neuropsychological development and trajectory of ADHD severity in early childhood. American Journal of Psychiatry.

OBJECTIVE: This longitudinal study examined if changes in neuropsychological functioning were associated with the trajectory of symptoms related to attention deficit hyperactivity disorder (ADHD) and impairment between preschool and school age. METHOD: The sample consisted of 3- and 4-year-old children (N=138) who were identified as being at risk for ADHD based on parent and teacher reports. Neuropsychological functioning was measured annually using the NEPSY at four time points (mean ages, 4.19, 5.36, 6.35, and 7.35 years). ADHD symptoms and impairment were assessed with semiannual parent and teacher reports using the ADHD Rating Scale-IV and the Children's Problems Checklist at 10 time points (mean ages at baseline and final assessment, 4.19 and 8.81 years, respectively). Hierarchical linear modeling was used to assess the trajectories of change in neuropsychological functioning and ADHD severity as well as the association of change in neuropsychological functioning with change in ADHD severity over time. RESULTS: Baseline neuropsychological functioning was not significantly associated with

the slope of change in ADHD severity. However, the magnitude of change in neuropsychological functioning was linearly associated with the trajectory of ADHD symptom severity and impairment, such that individuals with greater neuropsychological growth over time had a greater diminution of ADHD severity and impairment. Family socioeconomic status at baseline was significantly associated with initial ADHD severity and impairment, but not with change over time. CONCLUSIONS: Interventions that enhance neuropsychological functioning at an early age may be beneficial in attenuating long-term ADHD severity and impairment.

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Richa S, et al. 2014.

ADHD prevalence in Lebanese school-age population. Journal of Attention Disorders.

OBJECTIVE: The authors conducted an epidemiological study in Lebanon to estimate ADHD prevalence in school-age population. METHOD: They selected 1,000 children aged between 6 and 10 years, admitted in several schools in Lebanon. In each district, they randomly chose five schools, and in each school two classes. From each class, 10 children were included randomly in the population of the study. For each child, an ADHD-Rating Scale-IV School version was filled by a main teacher. The Home version was filled by the child's parents. RESULTS: The prevalence of ADHD Inattentive subtype was 3 per 1,000, Hyperactive-Impulsive subtype 12 per 1,000, and ADHD Combined subtype 17 per 1,000. ADHD was significantly more prevalent in boys than in girls. CONCLUSION: This is the first epidemiological study to be conducted in Lebanon to estimate the prevalence of ADHD among children.

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Riddle MA, et al. 2013.

The Preschool Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS) 6-year follow-up. Journal of the American Academy of Child & Adolescent Psychiatry.

OBJECTIVE: To describe the clinical course of attention-deficit/hyperactivity disorder (ADHD) symptom severity and diagnosis from ages 3 to 5 up to 9 to 12 years during a 6-year follow-up after the original Preschool ADHD Treatment Study (PATS). METHOD: A total of 207 participants (75% male) from the original PATS, assessed at baseline (mean age, 4.4 years, when all met criteria for ADHD) and 3 months later (before medication treatment), were re-evaluated in three follow-up assessment visits (year 3, mean age 7.4 years; year 4, 8.3 years; and year 6, 10.4 years). Parents and teachers rated symptom severity, and clinicians established psychiatric diagnoses. Analyses examined longitudinal changes in symptom severity and ADHD diagnosis. RESULTS: Parent- and teacher-rated symptom severity decreased from baseline to year 3 but remained relatively stable and in the moderate-to-severe clinical range through year 6. Girls showed generally steeper decreases in symptom T-scores. At

year 6, 89% (160/180) of remaining participants met ADHD symptom and impairment diagnostic criteria. Comorbidity of oppositional defiant disorder and/or conduct disorder was associated with a 30% higher risk of having an ADHD diagnosis at year 6 in the multiple logistic model. Medication status during follow-up, on versus off, did not predict symptom severity change from year 3 to year 6 after adjustment for other variables. CONCLUSIONS: ADHD in preschoolers is a relatively stable diagnosis over a 6-year period. The course is generally chronic, with high symptom severity and impairment, in very young children with moderate-to-severe ADHD, despite treatment with medication. Development of more effective ADHD intervention strategies is needed for this age group. Copyright 2013. Published by Elsevier Inc.

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Roke Y, et al. 2012.

Risk of hyperprolactinemia and sexual side effects in males 10-20 years old diagnosed with autism spectrum disorders or disruptive behavior disorder and treated with risperidone. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The aim of this study was to investigate the long-term treatment effects of risperidone on prolactin levels and prolactin-related side effects in pubertal boys with autism spectrum disorders (ASD) and disruptive behavior disorders (DBD). METHOD: Physical healthy 10-20-year-old males with ASD (n=89) and/ or DBD (n=9) chronically treated (mean 52 months, range 16-126 months) with risperidone (group 1, n=51) or not treated with any antipsychotic (group 2, n=47) were recruited to this observational study from the child psychiatry outpatient clinic. Morning non-fasting serum prolactin levels were measured and prolactin-related side effects were assessed by means of questionnaires and physical examination. Group differences were tested with Student's t, chi(2), Fisher exact, and Mann-Whitney tests, and logistic regression analysis, according to the type and distribution of data. RESULTS: Hyperprolactinemia was present in 47% of subjects in group 1 but only in 2% of subjects in group 2 (odds ratio 71.9; 95% CI, 7.7; 676.3). Forty-six percent of subjects in group 1 had asymptomatic hyperprolactinemia. Current risperidone dose and 9-OH risperidone plasma level were significant predictors of hyperprolactinemia (p=0.035 and p=0.03, respectively). Gynecomastia and sexual dysfunction were present in 43% and 14% of the subjects in group 1, respectively, compared with 21% and 0% of subjects in group 2 (p=0.05 and p=0.01). Gynecomastia was not significantly associated with hyperprolactinemia. CONCLUSIONS: Hyperprolactinemia is a common side effect in young males treated over the long term with risperidone. Young males treated with risperidone are more likely to report diminished sexual functioning than are those not treated with antipsychotics.

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Safren SA, et al. 2010.

Cognitive behavioral therapy vs relaxation with educational support for medication-treated adults with ADHD and persistent symptoms: a randomized controlled trial. JAMA.

CONTEXT: Attention-deficit/hyperactivity disorder (ADHD) in adulthood is a prevalent, distressing, and impairing condition that is not fully treated by pharmacotherapy alone and lacks evidence-based psychosocial treatments. OBJECTIVE: To test cognitive behavioral therapy for ADHD in adults treated with medication but who still have clinically significant symptoms. DESIGN, SETTING, AND PATIENTS: Randomized controlled trial assessing the efficacy of cognitive behavioral therapy for 86 symptomatic adults with ADHD who were already being treated with medication. The study was conducted at a US hospital between November 2004 and June 2008 (follow-up was conducted through July 2009). Of the 86 patients randomized, 79 completed treatment and 70 completed the follow-up assessments. INTERVENTIONS: Patients were randomized to 12 individual sessions of either cognitive behavioral therapy or relaxation with educational support (which is an attention-matched comparison). MAIN OUTCOME MEASURES: The primary measures were ADHD symptoms rated by an assessor (ADHD rating scale and Clinical Global Impression scale) at baseline, posttreatment, and at 6- and 12-month follow-up. The assessor was blinded to treatment condition assignment. The secondary outcome measure was self-report of ADHD symptoms. RESULTS: Cognitive behavioral therapy achieved lower posttreatment scores on both the Clinical Global Impression scale (magnitude -0.0531; 95% confidence interval [CI], -1.01 to -0.05; $P = .03$) and the ADHD rating scale (magnitude -4.631; 95% CI, -8.30 to -0.963; $P = .02$) compared with relaxation with educational support. Throughout treatment, self-reported symptoms were also significantly more improved for cognitive behavioral therapy (beta = -0.41; 95% CI, -0.64 to -0.17; $P < .001$), and there were more treatment responders in cognitive behavioral therapy for both the Clinical Global Impression scale (53% vs 23%; odds ratio [OR], 3.80; 95% CI, 1.50 to 9.59; $P = .01$) and the ADHD rating scale (67% vs 33%; OR, 4.29; 95% CI, 1.74 to 10.58; $P = .002$). Responders and partial responders in the cognitive behavioral therapy condition maintained their gains over 6 and 12 months. CONCLUSION: Among adults with persistent ADHD symptoms treated with medication, the use of cognitive behavioral therapy compared with relaxation with educational support resulted in improved ADHD symptoms, which were maintained at 12 months. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00118911.

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Saloner B, et al. 2013.

The impact of long-acting medications on attention-deficit/hyperactivity disorder treatment disparities. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: Long-acting stimulants have increased medication adherence for many children diagnosed with attention deficit/hyperactivity disorder (ADHD), but it is unknown whether the increase has been similar across racial/ethnic groups. Our objective was to determine whether differences in medication utilization and adherence among white, black, and Hispanic ADHD-diagnosed children and adolescents narrowed following the introduction of long-acting stimulants in the 1990s. METHODS: We conducted a retrospective analysis of Florida Medicaid claims data from fiscal years 1996-2005. At each of three cross sections, we identified children and adolescents 3-17 years of age with at least two claims with an ADHD diagnosis. We used linear regression to model disparities over the study period in utilization of any ADHD medications (utilization of long-acting medication specifically) and medication adherence, and identified patient level, treatment setting, and geographic contributors to

disparities. RESULTS: Although ADHD medication utilization was lower for ADHD-diagnosed minorities than whites in all years, minorities were as likely as whites to switch to long-acting medications. The increase in prescribed days following long-acting medication diffusion was comparable for white and black medication users (40 and 43 days, respectively), but lower for Hispanics (27 days). Geography and provider setting helped to explain disparities in medication utilization overall, but disparities in adherence were not explained by any of the covariates. CONCLUSIONS: Despite equivalent switching to long-acting medications in the study period, minorities continued to utilize all ADHD medications less than did whites, and for shorter periods. Provider setting helps explain the ADHD medication utilization gap. High-volume, minority-serving providers are potential targets for future interventions related to improved communication about medication and follow-up after medication initiation.

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Sciberras E, et al. 2011.

Predictors of parent-reported attention-deficit/hyperactivity disorder in children aged 6-7 years: a national longitudinal study. Journal of Abnormal Child Psychology.

This study examined the prenatal, postnatal and demographic predictors of parent-reported attention-deficit/hyperactivity disorder (ADHD) in an Australian population-based sample. Participants were families participating in the Longitudinal Study of Australian Children. There were approximately even numbers of males (51%) and females (49%) in the sample. Predictors of parent-reported ADHD status at Wave 2 (children aged 6-7 years) which were measured at Wave 1 (children aged 4-5 years) included cigarette smoking and alcohol use during pregnancy (prenatal factors); maternal postnatal depression, intensive care at birth, birth weight, and gestation (postnatal factors); and child gender, primary caregiver education, income, family composition, and maternal age at childbirth (socio-demographic factors). We found that male gender, cigarette smoking during pregnancy, and maternal postnatal depression were the only significant predictors (at the 5% level) of ADHD in the adjusted analysis (N=3,474). Our results are consistent with previous findings that male gender and cigarette smoking during pregnancy are risk factors for ADHD. In addition, we found that postnatal depression was predictive of parent-reported ADHD.

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Surman CB, et al. 2010.

Representativeness of participants in a clinical trial for attention-deficit/hyperactivity disorder? Comparison with adults from a large observational study. Journal of Clinical Psychiatry.

BACKGROUND: Clinical trials have demonstrated that pharmacotherapies can safely treat attention-deficit/hyperactivity disorder (ADHD) in adulthood. Eligibility criteria in these trials may significantly limit their external validity by excluding a significant portion of adults with ADHD

in the general population. In particular, exclusion criteria may frequently exclude individuals with comorbid mental health conditions, which are common in the adult ADHD population. METHOD: We addressed the representativeness of clinical trials by comparing 146 adult clinical trial participants with DSM-IV ADHD and a community sample composed of 124 adults with DSM-IV ADHD and 123 non-ADHD controls. Subjects were compared on socioeconomic status, Hollingshead occupational code, cognitive measures, lifetime psychopathology, and Global Assessment of Functioning (GAF) scale ratings. RESULTS: Adults with ADHD in the community sample had higher rates of lifetime psychiatric comorbidity, lower GAF scores, and lower occupational codes than those in the clinical trial. The clinical trial eligibility criteria would have excluded 61% of community sample adults with ADHD. This excluded portion of the community sample had higher rates of lifetime psychiatric comorbidity and lower GAF scores than clinical trial participants. CONCLUSIONS: Adults with ADHD participating in the clinical trial had less evidence of functional impairment and endorsed less psychiatric comorbidity than the majority of community sample subjects with ADHD. This suggests that findings from clinical trials may have limited external validity for adults with ADHD in the general population, particularly for those adults with ADHD with the greatest burden of comorbid psychopathology. Copyright 2010 Physicians Postgraduate Press, Inc.

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Tandon M, et al. 2011.

Preschool onset attention-deficit/hyperactivity disorder: course and predictors of stability over 24 months. Journal of Child & Adolescent Psychopharmacology.

OBJECTIVE: The present study examined the course of ADHD over 24 months in a preschool population. METHOD: n=48 preschoolers with ADHD, aged 3.0-5.11 years, subjects included in a larger sample of preschoolers with depression and other disorders (n=306) were comprehensively assessed at 3 annual time points over 24 months in a prospective longitudinal follow-up study. RESULTS: Baseline diagnoses of preschool MDD, ODD, and CD were risk factors for ADHD diagnosis over 24 months in this preschool population. Among older preschoolers and after controlling for key demographic variables, ADHD predicted later ADHD diagnosis, along with other significant risk factors - baseline diagnosis of ODD, and/or family history of disruptive disorders, and stressful life events. CONCLUSIONS: ADHD showed greater homotypic continuity at later rather than earlier preschool ages. Other disruptive comorbidities also emerged as key predictors of stable ADHD course. Study findings may help to inform which preschool ADHD populations to target for early intervention. Larger sample sizes are needed to confirm these findings and to further explore the stability, course, and predictors of outcome of preschool onset ADHD.

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Vitiello B, et al. 2012.

Blood pressure and heart rate over 10 years in the multimodal treatment study of children with ADHD. American Journal of Psychiatry.

OBJECTIVE: It is unknown whether prolonged childhood exposure to stimulant medication for the treatment of attention deficit hyperactivity disorder (ADHD) increases the risk for developing abnormalities in blood pressure or heart rate. The authors examined the association between stimulant medication and blood pressure and heart rate over 10 years. METHOD: A total of 579 children, ages 7-9, were randomly assigned to 14 months of medication treatment, behavioral therapy, the combination of the two, or usual community treatment. The controlled trial was followed by naturalistic treatment with periodic assessments. Blood pressure and heart rate data were first analyzed with linear regression models based on an intent-to-treat approach, using raw data and the blood pressure categories of prehypertension and hypertension. Currently medicated patients were then compared with never or previously medicated patients. Associations between cumulative stimulant exposure and blood pressure or heart rate were assessed. RESULTS: No treatment effect on either systolic or diastolic blood pressure could be detected. Children who were treated with stimulants had a higher heart rate (mean=84.2 bpm [SD=12.4] on medication alone and mean=84.6 bpm [SD=12.2] on medication plus behavioral therapy) than those who were treated with behavioral therapy alone (mean=79.1 bpm [SD=12.0]) or those who received usual community treatment (mean=78.9 bpm [SD=12.9]) at the end of the 14-month controlled trial, but not thereafter. Stimulant medication did not increase the risk for tachycardia, but greater cumulative stimulant exposure was associated with a higher heart rate at years 3 and 8. CONCLUSIONS: Stimulant treatment did not increase the risk for prehypertension or hypertension over the 10-year period of observation. However, stimulants had a persistent adrenergic effect on heart rate during treatment.

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Wender PH, et al. 2011.

A one year trial of methylphenidate in the treatment of ADHD. Journal of Attention Disorders.

OBJECTIVE: To determine the effects of long-term methylphenidate treatment on symptom severity and social adjustment in adult ADHD. METHOD: Adults (n = 116) meeting operational diagnostic criteria for ADHD (the "Utah Criteria") entered a randomized double-blind crossover trial of methylphenidate and placebo. Participants who improved on immediate-release methylphenidate entered a 12-month, open-label trial. Outcomes were assessed using the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDs), Clinical Global Impression-Improvement (CGI-I), global assessment of functioning (GAF), and the Weissman Social Adjustment Scale (WSAS). RESULTS: In the double-blind trial more patients improved (50% reduction of symptoms) receiving methylphenidate (74%) than placebo (21%, p = .001). During the open-label trial, symptom severity decreased 80% from baseline, and the WSAS decreased >50% in all subscales. The average GAF improved significantly (p < .0001). CONCLUSION: ADHD adults, who responded to methylphenidate in a short-term, placebo-controlled trial, responded to long-term treatment with marked improvements in ADHD symptoms and psychosocial functioning.

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Wiik KL, et al. 2011.

Behavioral and emotional symptoms of post-institutionalized children in middle childhood. Journal of Child Psychology & Psychiatry & Allied Disciplines.

BACKGROUND: Experience in institutional/orphanage care has been linked to increased mental health problems. Research suggests that children adopted from institutions experience specific difficulties related to inattention/overactivity. Evidence of internalizing and conduct problems relative to non-adopted peers has been found in early childhood and early adolescence, but problems may not differ from other adopted children. This study clarifies the understanding of behavioral and emotional symptoms of post-institutionalized (PI) children during middle childhood. METHODS: Eight- to eleven-year-old PI children (n=68) and two comparison groups, children internationally adopted from foster care (n=74) and non-adopted children (n=76), and their parents completed the MacArthur Health and Behavior Questionnaire related to attention-deficit/hyperactivity disorder (ADHD), externalizing, and internalizing symptoms. Group means for symptom level and number of children with symptoms above clinical cutoffs were compared. RESULTS: PI children displayed an increased level of ADHD symptoms per parent report. PI child and parent report indicated a higher number of PI children above clinical ADHD cutoff. Both groups of internationally adopted (IA) children had higher levels of externalizing symptoms relative to non-adopted children, with parent report indicating higher numbers of IA children above the externalizing clinical threshold. Informants differed in their report of internalizing symptoms. Parents indicated that both IA groups displayed increased internalizing symptom levels and greater numbers above clinical threshold; however, children reported this to be true only for the PI group. CONCLUSIONS: PI children differ from non-adopted peers across symptom domains in middle childhood. Whether these concerns were more broadly associated with international adoption rather than institutional care depended on symptom domain and informant. An understanding of this variability may be beneficial for treatment and intervention. 2010 The Authors. Journal of Child Psychology and Psychiatry. 2010 Association for Child and Adolescent Mental Health.

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Xu X, et al. 2010.

Racial differences in the effects of postnatal environmental tobacco smoke on neurodevelopment. Pediatrics.

OBJECTIVES: We used the 2001-2004 National Health and Nutrition Examination Survey to examine the association between postnatal environmental tobacco smoke exposure, measured as serum cotinine levels, and attention-deficit/hyperactivity disorder (ADHD) among children 4 to 15 years of age. We further investigated the interactions of race and serum cotinine levels with ADHD. METHODS: Logistic regression models

were used to evaluate associations. RESULTS: This study found that the prevalence of ADHD increased as blood cotinine levels increased. The effects of blood cotinine levels on ADHD differed according to race. Compared with children of the same racial group with the lowest blood cotinine levels, the odds ratios were 2.72 (95% confidence interval: 1.25-5.93) for Mexican American children and 5.32 (95% confidence interval: 1.55-18.3) for children in other racial groups with the highest blood cotinine levels, with controlling for the effect of maternal smoking during pregnancy. However, no significant associations between blood cotinine levels and ADHD were observed among non-Hispanic white or non-Hispanic black children. CONCLUSIONS: The findings of this study underscore the possibility of racial disparities in the effects of environmental tobacco smoke on behavioral problems in children. These findings warrant further investigation.

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Zima BT, et al. 2010.

Quality of care for childhood attention-deficit/hyperactivity disorder in a managed care medicaid program. Journal of the American Academy of Child & Adolescent Psychiatry.

OBJECTIVE: To examine whether clinical severity is greater among children receiving attention-deficit/hyperactivity disorder (ADHD) care in primary care compared with those in specialty mental health clinics, and to examine how care processes and clinical outcomes vary by sector across three 6-month time intervals. METHOD: This was a longitudinal cohort study of 530 children aged 5 to 11 years receiving ADHD care in primary care or specialty mental health clinics from November 2004 through September 2006 in a large, countywide managed care Medicaid program. RESULTS: Clinical severity at study entry did not differ between children who received ADHD care in solely primary or specialty mental health care clinics. At three 6-month intervals, receipt of no care ranged from 34% to 44%, and unmet need for mental health services ranged from 13% to 20%. In primary care, 80% to 85% of children had at least one stimulant prescription filled and averaged one to two follow-up visits per year. Less than one-third of children in specialty mental health clinics received any stimulant medication, but all received psychosocial interventions averaging more than five visits per month. In both sectors, stimulant medication refill prescription persistence was poor (31%-49%). With few exceptions, ADHD diagnosis, impairment, academic achievement, parent distress, and parent-reported treatment satisfaction, perceived benefit, and improved family functioning did not differ between children who remained in care and those who received no care. CONCLUSION: Areas for quality improvement are alignment of clinical severity with provider type, follow-up visits, stimulant use in specialty mental health, agency data infrastructure to document delivery of evidence-based psychosocial treatment, and stimulant medication refill prescription persistence. Copyright 2010 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. All rights reserved.

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Zoega H, et al. 2012.

A population-based study of stimulant drug treatment of ADHD and academic progress in children. Pediatrics.

OBJECTIVE: We evaluated the hypothesis that later start of stimulant treatment of attention-deficit/hyperactivity disorder adversely affects academic progress in mathematics and language arts among 9- to 12-year-old children. **METHODS:** We linked nationwide data from the Icelandic Medicines Registry and the Database of National Scholastic Examinations. The study population comprised 11,872 children born in 1994-1996 who took standardized tests in both fourth and seventh grade. We estimated the probability of academic decline (drop of > 5.0 percentile points) according to drug exposure and timing of treatment start between examinations. To limit confounding by indication, we concentrated on children who started treatment either early or later, but at some point between fourth-grade and seventh-grade standardized tests. **RESULTS:** In contrast with nonmedicated children, children starting stimulant treatment between their fourth- and seventh-grade tests were more likely to decline in test performance. The crude probability of academic decline was 72.9% in mathematics and 42.9% in language arts for children with a treatment start 25 to 36 months after the fourth-grade test. Compared with those starting treatment earlier (< 12 months after tests), the multivariable adjusted risk ratio (RR) for decline was 1.7 (95% confidence interval [CI]: 1.2-2.4) in mathematics and 1.1 (95% CI: 0.7-1.8) in language arts. The adjusted RR of mathematics decline with later treatment was higher among girls (RR, 2.7; 95% CI: 1.2-6.0) than boys (RR, 1.4; 95% CI: 0.9-2.0). **CONCLUSIONS:** Later start of stimulant drug treatment of attention-deficit/hyperactivity disorder is associated with academic decline in mathematics.

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Zoega H, et al. 2012.

Age, academic performance, and stimulant prescribing for ADHD: a nationwide cohort study. Pediatrics.

BACKGROUND: We evaluated whether younger age in class is associated with poorer academic performance and an increased risk of being prescribed stimulants for attention-deficit/hyperactivity disorder (ADHD). **METHODS:** This was a nationwide population-based cohort study, linking data from national registries of prescribed drugs and standardized scholastic examinations. The study population comprised all children born in 1994-1996 who took standardized tests in Iceland at ages 9 and 12 (n = 11 785). We estimated risks of receiving low test scores (0-10th percentile) and being prescribed stimulants for ADHD. Comparisons were made according to children's relative age in class. **RESULTS:** Mean test scores in mathematics and language arts were lowest among the youngest children in the fourth grade, although the gap attenuated in the seventh grade. Compared with the oldest third, those in the youngest third of class had an increased relative risk of receiving a low test score at age 9 for mathematics (1.9; 95% confidence interval [CI] 1.6-2.2) and language arts (1.8; 95% CI 1.6-2.1), whereas at age 12, the relative risk was 1.6 in both subjects. Children in the youngest third of class were 50% more likely (1.5; 95% CI 1.3-1.8) than those in the oldest third to be prescribed stimulants between ages 7 and 14. **CONCLUSIONS:** Relative age among classmates affects children's academic performance into puberty, as well as their risk of being prescribed stimulants for ADHD. This should be taken into account when evaluating children's performance and behavior in school to prevent unnecessary stimulant treatment.

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Zuvekas SH, et al. 2012.

Stimulant medication use in children: a 12-year perspective. American Journal of Psychiatry.

OBJECTIVE: The authors examined the utilization of stimulant medications for the treatment of ADHD in U.S. children during the period 1996-2008 to determine trends by age, sex, race/ethnicity, family income, and geographic region. METHOD: The 1996-2008 database of the Medical Expenditure Panel Survey, a nationally representative annual survey of U.S. households, was analyzed for therapeutic stimulant use in children age 18 and younger. The data for 1987 were also recalculated for reference. RESULTS: An estimated 3.5% (95% confidence interval=3.0-4.1) of U.S. children received stimulant medication in 2008, up from 2.4% in 1996. Over the period 1996-2008, stimulant use increased consistently at an overall annual growth rate of 3.4%. Use increased in adolescents (annual growth, 6.5%), but it did not significantly change in 6- to 12-year-olds, and it decreased in preschoolers. Use remained higher in boys than in girls, and it remained consistently lower in the West than in other U.S. regions. While differences by family income have disappeared over time, use of stimulants in ADHD treatment is significantly lower in racial/ethnic minorities. CONCLUSIONS: Overall, pediatric stimulant use has been slowly but steadily increasing since 1996, primarily as a result of greater use in adolescents. Use in preschoolers remains low and has declined over time. Important variations related to racial/ethnic background and geographic region persist, thus indicating a substantial heterogeneity in the approach to the treatment of ADHD in U.S. communities.

Appendix G: Summary Table

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
Key Question 1: Effectiveness of interventions for ADHD and Disruptive Behavior Disorders (DBD) in children younger than 5 years of age			
<p>Parent Behavior Training: Parent behavioral interventions are an efficacious treatment option for preschoolers with DBD and show benefit for ADHD symptoms. Studies support the long-term effectiveness of parent interventions for preschoolers with DBD, including ADHD symptoms, with evidence that benefits are maintained for up to 2 years. There also appears to be a dose-response effect.</p>	Conclusion is up to date	No new research was found	All three experts agreed that the conclusion is still valid
<p>Multicomponent Home and School or Daycare-Based Interventions: Evidence is drawn from few reports.</p> <p>Where there is no socioeconomic burden, multicomponent interventions work as well as a structured parent education program in several domains.</p> <p>Where there is socioeconomic burden, the treatment classroom appears to be the primary beneficial intervention,</p>	Conclusion is up to date	<p>One year follow up study of the Incredible Years interventions found that 22 of 27 variables that showed post-treatment effects were maintained, with 70-75% falling below clinical cutoffs for externalizing behaviors (50% at baseline), and more than 50% fell below clinical cutoffs for hyperactivity and inattentiveness (all in clinical range at baseline).³</p> <p>A long term follow up to the PATS study found that parent and teacher rated severity decreased from baseline to year three, then remained stable in the moderate to severe clinical range through year 6. Girls showed generally steeper decreases</p>	All three experts agreed that the conclusion is still valid.

Appendix G: Summary Table

Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
and this appears to be related to lack of parent engagement and attendance at parent behavior training (PBT) sessions. Relative benefits of the school-based intervention diminished over 2 years.		in symptom T-scores. At year 6, 89% (160/180) of remaining participants met ADHD symptom and impairment diagnostic criteria. ⁶	
Medication: MPH: With evidence drawn primarily from the Preschool ADHD Treatment Study (PATS) study, Methylphenidate (MPH) (e.g., short-acting, immediate-release MPH) is both efficacious and generally safe for treatment of ADHD symptoms, but there has been no long-term followup in preschoolers.	Conclusion is possibly out-of-date regarding safety	No new research was found.	All three experts agreed that this conclusion is still valid.
Key Question 2: Long-term (>1 year) effectiveness of interventions for ADHD in people 6 years and older			
Medication Treatment: MPH, ATX (SOE low): Very few studies include untreated controls. Studies were largely funded by industry. Psychostimulants continue to provide control of ADHD symptoms and are generally well tolerated for months to years at a time. The evidence for MPH use in the context of	Conclusion is possibly out-of-date regarding safety	A study conducted in Norway surveyed adults who had been treated with ADHD medication and found that pharmacologic treatment for more than two years was associated with better functioning (Adult ADHD Self-Report Scale and Mental Health Index-5) than treatment for two years or less. ⁷ A study in Italy examining the long term effects of MPH or ATX on growth in ADHD drug naïve children found that both ATX and MPH lead	Two experts agreed that the conclusion was still valid. One expert suggested the study by Lensing et al. ⁷ in adults, and that the study quality may not be sufficient to change the conclusions of the original CE

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
<p>careful medication monitoring shows good evidence for benefits for symptoms for 14 months. Atomoxetine (ATX) is effective for ADHD symptoms and well tolerated over 12 months.</p>		<p>to decreased height gain, with a significantly higher effect for ATX than for MPH; however, the difference between groups was only significant during the first year of treatment. For both ATX and MPH there was a slowed rate of weight gain for both drugs that was significantly higher for ATX than MPH.⁸</p> <p>Another study examining cardiovascular effects of ATX and MPH performed blood pressure, heart rate, and ECG assessments at six month intervals for 24 months and increases in blood pressure and heart rate at 6 and 12 months with both ATX and MPH, with a higher probability for MPH.⁹</p>	
<p>Medication Treatment: GXR (SOE Insufficient): Only one study of guanfacine extended release (GXR) monotherapy is available. It reports reduced ADHD symptoms and global improvement, although less than a fifth of participants completed 12 months. Monitoring of cardiac status may be indicated since approximately 1% of participants showed ECG changes judged clinically significant.</p>	<p>Conclusion is up to date</p>	<p>A study conducted in Norway surveyed adults who had been treated with ADHD medication and found that pharmacologic treatment for more than two years was associated with better functioning (Adult ADHD Self-Report Scale and Mental Health Index-5) than treatment for two years or less.⁷</p>	<p>Two experts agreed that the conclusion was still valid. One expert suggested the study by Lensing et al.⁷ in adults, and that the study quality may not be sufficient to change the conclusions of the original CE</p>

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
Medication Treatment: LDX. (no studies)		A one-year study of the safety and effectiveness of LDX in adolescents found improvement on the YQOL-R and ADHD-RS-IV, and no significant EEG or vital sign changes. ¹⁰	
<p>Combined Psychostimulant Medication and Behavioral Treatment: The results from 2 cohorts indicate both medication (MPH) and combined medication and behavioral treatment are effective in treating ADHD plus ODD symptoms in children, primarily boys ages 7-9 years of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment.</p> <p>Several reports from one high-quality study suggest that combined medication and behavioral treatment improves outcomes more than medication alone for some subgroups of children with ADHD combined type and for some outcomes.</p>	Conclusion is up to date	No new research was found	All three experts agreed that the conclusion is still valid.
<p>Behavioral/Psychosocial: There is insufficient evidence to draw conclusions on long term</p>	Conclusion is up to date	No new research was found.	All three experts agreed that the conclusion is still valid.

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
outcomes for persons 6 years and older with a diagnosis of ADHD.			
Parent Behavior Training: There is insufficient evidence to draw conclusions for persons 6 years and older with a diagnosis of ADHD.	Conclusion is up to date	A study comparing MPH to MPH + parent training examined participants at one-year follow up and found that there were no significant effects associated with the addition of parent training. ¹¹	All three experts agreed that the conclusion is still valid.
Academic Interventions: One good-quality study and its extension showed that classroom-based programs to enhance academic skills are effective in improving achievement scores in multiple domains, but following discontinuation, the benefits for sustained growth in academic skills are limited to the domain of reading fluency. All other domains show skill maintenance but not continued growth.	Conclusion is up to date	No new research was found.	All three experts agreed that the conclusion is still valid.
Key Question 3: Underlying prevalence of ADHD, rates of diagnosis, and treatment by geography, time period, provider type characteristics			
Prevalence (Geography): Context and cultural overlay influence how ADHD is understood from country to country, and thus how it is treated. Underlying prevalence does not	Conclusion is up to date	One study examined the prevalence of ADHD in Lebanon and found that The prevalence of ADHD Inattentive subtype was 3 per 1,000, Hyperactive-Impulsive subtype 12 per 1,000, and ADHD Combined subtype 17 per 1,000. ¹²	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children’s Health 2011 and found that fewer children in the West under 18 had ever diagnosed (8.1%), had a current

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
appear to vary much between nations and regions, once differences in methodologies for ascertainment are taken into account			diagnosis (6.4%), with the high rates in the South (12.6%; 10.1%)
<p>Prevalence (Time period): Since identified as a clinical entity in 1902 in the context of mandatory education, prevalence of cases identified has increased. Some proportion of this secular trend is due to refinement of the state of knowledge, as well as changes in definition of acceptable informant, uses of screening tests, and changes in classification systems and diagnostic categories over time. In addition, patterns of access and location of service have been used to document prevalence.</p>	Conclusion is up to date	No new research was found	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children’s Health 2007 and 2011 and found that between 2007 and 2011, ADHD diagnoses increased from 7.8% to 11% for those ever diagnosed, and 7.2% to 8.8% in 2007 to 8.8% in 2011 for current diagnoses.
<p>Prevalence (SES): Some studies suggest that those of lower SES have a higher prevalence of ADHD, although those of higher socioeconomic status (SES) are more likely to be treated.</p>	Conclusion is up to date	No new research was found	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children’s Health 2007 and 2011 and found that rates of ADHD were highest in households below the federal poverty level and lowest in those greater than 200% of the federal poverty level. Rates were the highest among those living in households with

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
			years of education (higher than both more and less education), with the lowest rates from households with less than 12 years. Rates were significantly higher among children with any health insurance coverage, with the highest rates among those covered by Medicaid.
Prevalence (Sex): Most studies illustrate a sex difference in the prevalence of ADHD (males > females).	Conclusion probably out-of-date regarding adults	One study of the Early Childhood Longitudinal Study found ¹⁴ that being male increased the risk of an ADHD diagnosis. Another study found that in Germany, the standardized age prevalence and incidence of new diagnoses were 3-4 times higher for males than females 3-17 years old. ¹⁵	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children's Health 2011 and found that males were more likely to have a current or previous diagnosis.
Prevalence (Age): The age group ≈5-10 years appears to experience the highest prevalence. ADHD research detailing prevalence in adults is lacking	Conclusion is probably out-of-date	No new research was found	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children's Health 2011 and found that among children under 18, those aged 5-10 had the lowest rates of ever being diagnosed with ADHD (7.7%) having a current diagnosis (6.8%) with the highest rates among 1-4 year olds (14.3%; 11.4%).

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
<p>Prevalence (Race/Ethnicity): Prevalence rates are lower in African American and Hispanic children as compared with Whites.</p>	<p>No information</p>	<p>One study found¹⁴ that being White and being raised in an English-speaking household increased the risk of an ADHD diagnosis. Another study of children aged 5-11 years at Kaiser in Southern California found that children diagnosed with ADHD were more likely to be White or African American.¹⁶</p>	<p>Two experts agreed that the conclusion was still valid. One expert suggested a study¹³ which examined data from the National Survey of Children’s Health 2011 and found that rates were similar between White and Black children under 18, and significantly higher than all other races. Rates in Hispanic/Latinos were significantly lower than in White and Hispanic/Latinos. Rates were significantly higher among those who spoke English at home.</p>
<p>Treatment (Location): Rates of treatment vary considerably due to location and access to providers of health care services, internationally as well as regionally or even within the same community, dependent on provider type and availability, provider remuneration, and insurance status of patient.</p>	<p>Conclusion is up to date</p>	<p>No new research was found</p>	<p>Two experts agreed that the conclusion was still valid. One expert suggested a study¹³ which examined data from the National Survey of Children’s Health 2011 and found that fewer children in the West under 18 were on medication (3.8%); with the highest rates in the South (7.3%)</p>
<p>Treatment (Provider): Family practitioners in many jurisdictions, particularly those with limited access to specialists, report significant pressure from parents and teachers to prescribe stimulant</p>	<p>Conclusion is up to date</p>	<p>No new research was found</p>	<p>All three experts agreed that the conclusion is still valid.</p>

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
medications.			
<p>Treatment (Informant): The sociocultural experience of the parent or teacher informant may influence interpretation and reporting of behaviors, willingness and persistence in seeking professional help, and/or the acceptance of treatment. Accuracy and completeness of data influence prevalence estimates, as health insurance and prescription administrative databases suggest greater increase in treatment with medications over time than repeated community surveys do.</p>	Conclusion is up to date	No new research was found	All three experts agreed that the conclusion is still valid.
<p>Treatment (Time): The rate of psychostimulant medication has increased over the past 3 decades. More recent statistics from the International Narcotics Control Board, using a denominator of standardized defined daily doses (S-DDD), reports that medical use of MPH (i.e., Ritalin) in the United States has increased from 7.14 S-DDDs per 1,000 inhabitants per day in 2004 to 12.03 S-DDDs per 1,000 inhabitants per</p>	Conclusion is up to date	No new research was found	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children's Health 2011 and found that between 2004 and 2011, rates of medication for ADHD increased from 4.8% to 6.1%.

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
day in 2008. ¹			
<p>Treatment (SES): Children of lower SES are identified as having ADHD more often than children of higher SES; however, the latter are more likely to receive stimulant medications. Lower SES and minority ethnicity are associated with shorter duration of medication use. Insurance status may influence access to specialist providers in the United States.</p>	Conclusion is up to date	No new research was found	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children's Health 2011 and found that children under 100% (PR = 1.22) and between 100-200% (PR = 1.16) of poverty were more likely to be treated with medication than children >200% poverty, and children receiving public health insurance (PR = 1.52) were more likely to be treated than those with private insurance, with uninsured children the least likely to be treated (PR = 0.42).
<p>Treatment (Sex): Only sparse comparative data are available examining rates of treatment by sex once ADHD is diagnosed.</p>	Conclusion is up to date	One study found that in Germany, there was little difference in drug treatment among females and males 3-17 years old. ¹⁵ A German study examining usage patterns of MPH and ATX found that drug treatment was more common in boys than girls and that girls discontinued treatment earlier than boys. ¹⁷	Two experts agreed that the conclusion was still valid. One expert suggested a study ¹³ which examined data from the National Survey of Children's Health 2011 and found that males were 2.31 times more likely to be treated with medication.

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Conclusions From CER Executive Summary	Conclusions from Most Recent Surveillance Assessment (July 2012 – Link to Paper)	SRC Literature Search	Expert Opinion
<p>Treatment (Age): Medication treatment prevalence is higher for primary school-age children than for adolescents or adults.</p>	<p>Conclusion is up to date for U.S.</p>	<p>A national study in Iceland examined age within grades, and found that children in the youngest third of class were 50% more likely (1.5; 95% CI 1.3-1.8) than those in the oldest third to be prescribed stimulants between ages 7 and 14.¹⁸</p>	<p>Two experts agreed that the conclusion was still valid. On expert suggested a study¹³ which examined data from the National Survey of Children’s Health 2011 and found that among children under 18, those aged had the lowest rates of current being on medication for ADHD (4.9%), with the highest rates among 11-14 year olds (8.0%)</p>
<p>Treatment (Race/Ethnicity): Caucasian children are twice as likely to use stimulants as either Hispanic or African American children, and minority ethnicity is associated with shorter duration of medication use.</p>	<p>No information</p>	<p>One study¹⁹ analyzed FL Medicare claims data and found that despite equivalent switching to long-acting medications in the study period, minorities continued to utilize all ADHD medications less than did whites, and for shorter periods. Another study of children aged 5-11 years at Kaiser in Southern California found that children who had received more than two prescriptions specific to ADHD were more likely to be White or African American.¹⁶</p>	<p>Two experts agreed that the conclusion was still valid. On expert suggested a study¹³ which examined data from the National Survey of Children’s Health 2011 and found that medication rates were lower in Black (0.8 and other racial minorities (0.4) as compared with Whites, and rates were significantly higher Whites than in Hispanics (PR = 0.44) and children whose primary language at home was not English (PR = 0.14).</p>