Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder in School-Age Children and Adolescents
2014 Clinical Practice Guideline

This guideline is informational only. It is not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient’s needs on an individual basis.

Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Approved by the National Guideline Directors March 2014
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Introduction

Kaiser Permanente’s National Guideline Program

The National Guideline Program (NGP) supports the development of a core set of explicit, evidence-based clinical practice guidelines, practice resources, and evidence synopses to assist Kaiser Permanente (KP) physicians, administrators, and other health care professionals in determining the most effective medical practices.

This core set of evidence-based resources will:

- Create Programwide economies of scale,
- Support ongoing performance improvement activities,
- Consistently provide high quality resources for use in care delivery tools and systems, and
- Increase KP regions’ abilities to leverage clinical guidelines to improve clinical outcomes.

Clinical practice guidance, based on scientific evidence, is essential for providing high quality care and continuously improving on it. Such guidance needs to be integrated into the electronic medical record and other decision support tools to be accessible to clinicians at the point of care. In addition, engaging our members in collaborative, shared decision-making conversations regarding their personal preferences is an essential component of patient-centered quality care. Furthermore, cost-effectiveness of various evidence-based interventions and resource limitations are important considerations. This involves addressing health problems in ways that maximize the health of the population given the available resources.

Who are the National Guideline Directors?

The National Guideline Directors group (NGD) oversees the KP National Guideline Program. The NGD selects and approves topics for development of evidence-based knowledge products and is responsible for maintaining the process, including quality assurance and methodological standards, for development of the clinical recommendations for clinical guidance.

The NGD has established an overall quality control mechanism to ensure adherence to the methods and processes described in this document, and that the labels applied to the quality of the evidence and the strength of the recommendation are consistent with the underlying evidence and explicitly justified. While ultimate responsibility for the quality of KP’s National Guidelines rests with the National Guideline Directors, the NGD has delegated quality control to the Guideline Quality Committee.
What Is the Guideline Quality Committee?

The Guideline Quality (GQ) Committee is a subcommittee of the National Guideline Directors and is comprised of clinical evidence specialists and physician methodologists with expertise in clinical epidemiology, biostatistics, and research methodology. Final review and approval of all national recommendations, whether internally or externally developed, has been delegated to the GQ by the National Guideline Directors.

Why is it Important for a Guideline to Be Evidence-Based?

The Kaiser Permanente National Guideline Program (NGP) provides the organization with evidence-based clinical recommendations to support care delivery and optimize the health of Kaiser Permanente (KP) members. When based on a rigorous methodology, clinical practice recommendations are essential tools for improving quality of care; they support KP physicians, other health care professionals, and administrators in their quest to provide the highest quality of care through the consistent delivery of effective clinical practices. When implemented, these practices help to reduce unwarranted variation in care and improve clinical outcomes.

How Are Guidelines Developed?

The three major pathways used to develop KP clinical recommendations:

<table>
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<th>Pathway</th>
<th>Description</th>
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<tr>
<td>Existing guideline</td>
<td>Specialty Chiefs, other provider groups, or Guideline Development Team (GDT) members may identify familiar and valued sources of external guidelines. The GDT, utilizing approved criteria, may propose guideline recommendations from an external organization as an appropriate starting point for guideline development.</td>
</tr>
<tr>
<td>Existing systematic review</td>
<td>When no acceptable external guidelines are identified, the lead team systematically identifies and reviews relevant systematic reviews, meta-analyses and original studies.</td>
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<tr>
<td>Internal systematic review</td>
<td>If no existing guidelines or systematic reviews are identified, then an internally generated systematic review of the literature is conducted.</td>
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One appropriate starting point for guideline development is the adopting or adapting of an external guideline or recommendation(s) taken from an external guideline. This ADHD guideline, initiated in 2011, has been primarily developed by adapting the process suggested by the ADAPTE Collaboration. As such, the guideline is based on the 2009 KP National ADHD guideline and two external guidelines: *Child/Adolescent Attention Deficit/Hyperactivity Disorder (ADHD) Clinical Practice Guideline* by Kaiser Permanente (KP) 2009, *Management of Attention Deficit and Hyperkinetic Disorders in Children and Young People: A National Clinical Guideline* by Scottish Intercollegiate Guidelines Network (SIGN) 2009, and *Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People and Adults* by National Institute for Health and Clinical Excellence (NICE) 2009. After extensive evaluation during its 3-year review and update cycle, the NICE guideline developers reached a decision in November 2011 that the guideline would not be updated at the time, but will be reviewed in July 2014.

To develop this guideline, CMI consultants work with a multidisciplinary Guideline Development Team (GDT). Each GDT consists of a core group of physicians, representing primary care and the specialties most affected by the guideline topic, and, as appropriate, other content experts from disciplines such as pharmacy, nursing, and health education. The members of a GDT are nominated by the respective National Guideline Directors to represent their regions.

After the Guideline Development Team (GDT) and other subject matter experts are solicited for their external guideline suggestions, CMI consultants proceed with the ADAPTE process by defining the guideline scope and clinical questions. A systematic literature search is conducted to identify guidelines that satisfy the search parameters. To conduct an initial screening, three independent guideline development leaders evaluate and subsequently reconcile the rigor of development using the AGREE II instrument for each identified guideline. Only guidelines that receive a rigor score greater than the scaled final score of 60% - based on ADAPTE - were fully evaluated using the AGREE II instrument. These guidelines are then used to create a recommendation matrix to align the selected clinical questions within the defined scope in the KP guideline with those in the identified external guidelines. Once the most rigorous guidelines have been selected, each evaluator examines and independently rates the other five AGREE II domains: scope and purpose, stakeholder involvement, clarity of presentation, applicability, and editorial independence. The evaluators then reconcile their scores and comments by domain, which allows for a calculation of domain-specific final scaled scores.

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* The ADAPTE process calls for the 1) identification of external guidelines, the determination of congruency with identified clinical questions, analysis of appropriate guidelines for quality, and the rendering of adaptations as needed to fit KP practices and populations.

† For more information, please see [NICE’s rationale for not conducting a review in 2011](#).
All external guidelines that receive scores of 60% and above are considered rigorous and used to adopt/adapt recommendations for the updated ADHD guideline. CMI consultants rely heavily on GDT expertise when drafting recommendation modifications, which target the specific needs and circumstances of KP and its members. All evidence-based recommendations are provided an evidence grade. For additional information on evidence grading, see Appendix A.

The GDT reviews the appraisal of the evidence and develops or revises clinical recommendations based on the current evidence. Each regional representative then presents the draft guideline recommendations to key experts and champions in their regions for critical review and support to improve the likelihood of implementation once the guideline is published.

**How Often Are Guidelines Reviewed and Revised?**

Clinical recommendations development at Kaiser Permanente follows an evidence-based, systematic, and transparent process. In order to ensure that recommendations are high-quality, relevant, and accurately reflect the body of the evidence, the guideline development process includes the following sequential steps:

1. Determine the scope of the clinical content to be addressed in the guideline.
2. Develop the key clinical questions, including specification of patient populations, comparative interventions and outcomes.
3. Identify and evaluate existing recommendations and guidelines.
4. Conduct a comprehensive search of relevant databases and other sources to identify relevant evidence.
5. Screen, select and extract data from studies.
6. Critically appraise the strengths and limitations of the identified studies.
7. Assess, synthesize and grade of the body of evidence.
8. Develop recommendations and rationale statements that are consistent with the evidence.
10. Approve guideline.
11. Disseminate and implement guideline.
12. Periodically update the evidence.

To develop the ADHD guideline, released in February 2012, a multidisciplinary, interregional GDT met in April 2011 to define the scope of the guideline. The Project Management Team then performed systematic reviews of the medical literature for each clinical question identified by the GDT, assembled and presented the evidence, and developed draft recommendations for review by the GDT. The GDT then carefully reviewed the recommendations and supporting evidence in a series of meetings from August 2011 through November 2011. The Guideline Quality (GQ) Committee examined and approved the guideline in February 2012. The guideline was reviewed and re-approved in March 2014.
What Does It Mean for a Guideline to Be Evidence-Based?
An evidence-based guideline consists of rigorously developed recommendations and rationale statements, which result from a systematic evaluation and synthesis of the literature. Currently, four paths qualify a guideline to be evidence-based:

1. Determining a settled evidence base, which is indicated by one or more of the following:
   - Presence of an evidence base in which further research is unlikely to be done.
   - Presence of high-quality systematic reviews or meta-analyses, or presence of studies, such that further research is unlikely to change confidence in the estimate of effect (e.g., meets GRADE criteria for high overall quality of evidence across outcomes).
   - No new evidence or development of sufficient importance to significantly change the Clinical question/Recommendation(s).

2. Adopting or adapting a known high-quality guideline, which has undergone careful evaluation of its scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence.

3. Systematic review of the evidence that underlie the recommendations when no acceptable external guidelines are identified.

4. Internally generated systematic review that underlie the recommendations when no acceptable external guidelines or systematic reviews are identified.

What Does It Mean for a Guideline to Be Approved and National?
Final review and approval of all KP national guidelines, whether internally or externally developed, has been delegated to the Guideline Quality (GQ) Committee by the National Guideline Directors. “Approved by the National Guideline Directors” means that the GQ has reviewed and approved the final recommendations, rationale statements, and evidence summaries.

Once approved, the Project Manager sends NGD-approved guidelines to the Regional guideline directors and managers for distribution within their respective regions. These eight regions may modify the guidelines to fit the Regional environment. The Regional guidelines are sent to clinicians, physician assistants, nurse practitioners, and other health care professionals in relevant specialty groups, as well as Health Plan and Hospital operations, administrative and education staff, providers by email, through regional physician portals and by US mail for clinicians not connected to the Kaiser Permanente email system.
Contact information

Douglas Newton, MD  
ADHD Clinical Lead  
Care Management Institute  
E-mail: Douglas.A.Newton@kp.org

Jill Haynes, MPH  
Care Management Consultant  
Care Management Institute  
E-mail: Jill.Haynes@kp.org

Acknowledgments

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KP ADHD Guideline Project Management Team

Douglas Newton, MD  
Clinical Lead  
KP Colorado

Jill Haynes, MPH  
Project Manager  
Care Management Institute

Donald Fong, MD  
EBM Methodologist  
KP Southern California
KP ADHD Guideline Development Team

There were no conflicts of interests for any member of the Guideline Development Team (GDT).

**Colorado**
Bruce C. Doenecke, MD - Pediatrician
Kerri M. Gaughan, PharmD - Clinical Pharmacy Specialist, Behavioral Health
Edward Gibson, MD - Mental Health Pediatrician/Psychiatrist

**Georgia**
Catherine Dragstedt, MD - Chief of Pediatrics
Alice Heimberg-Funk, MD - Child and Adolescent Psychiatrist

**Hawaii**
John Draeger, MD - Chief BHS, Psychiatrist

**Northern California**
Anna O. Wong, PhD - Psychologist

**Northwest**
Heather N Block, MPH - Prevention Services Manager
Shannon Ann Brown, MD - Physician, Pediatrics
Corinne Gavrun, PharmD, MBA - Drug Information and Formulary Pharmacist
Heather Jones, MD - Child Psychiatrist, Team Leader
Lisa J. Nakashimada, RPh - Medication Management, Clinical Pharmacy Services

**Ohio**
Larissa Elgudin, MD - Child/Adolescent Psychiatrist
William Wieder, MD

**Program Offices - CMI**
Andrew Bertagnolli, PhD - Principal Consultant, Behavioral Health & Pain Management
Gladys I Tom - Principal Consultant, Evidence Services

**Southern California**
Jessica A. Lam, MPH - Consultant, Medical Technology Assessment and Guidelines
Robert A. Moss, MD - Pediatrician
David G. Reynolds - Chief of Psychiatry
Guideline Summary

1. Clinicians should not universally screen children and adolescents for ADHD. *(Strong recommendation)*

2. Clinicians should evaluate children and adolescents for ADHD when they have signs, symptoms, or impairment suggestive of ADHD. *(Strong recommendation)*

3. As part of the evaluation and diagnosis of ADHD in children and adolescents, clinicians should use structured, validated rating scales,* and refer to and follow the DSM-5 diagnostic criteria. *(Strong recommendation)*

4. Clinicians should conduct a baseline physical assessment (including measurement of pulse, blood pressure, weight and height with the appropriate use of percentile charts) prior to initiating pharmacological therapy. *(Strong recommendation)*

5. Clinicians may recommend cardiac risk evaluation or consultations prior to prescribing psychostimulants for children and adolescents with ADHD with known cardiac abnormalities. *(Weak recommendation)*

6. Clinicians should not perform psychodiagnostic tests as part of ADHD evaluation in the absence of other indications. *(Strong recommendation)*

7. In the absence of signs or symptoms of atopy, clinicians should not refer children and adolescents with ADHD for allergy evaluation, as it is unlikely to change the diagnosis or treatment plan. *(Weak recommendation)*

* The publicly available Vanderbilt ADHD Rating Scales are recommended as part of the evaluation and diagnosis of ADHD in children and adolescents. The following behavioral rating scales are options to be used in addition to the initial evaluation: Conners’ Rating Scales (the revised Conners’ Parent Rating Scale (CPRS-R), the revised Conners’ Teacher Rating Scale (CTRS-R), and the Conners’/Wells Self-Report of Symptoms rating scale (CASS)), Achenbach Scales: CBCL, TRF, YSR, ADHD Rating Scale – IV (ADHD RS-IV) (DSM-5-based), Swan, Nolan, and Pelham Questionnaire (SNAP) (DSM-5-based), and Achenbach and Vanderbilt behavioral rating scales can be utilized to assess some comorbid disorders.
8. First-line pharmacological treatment
   a) Clinicians should recommend stimulant medications methylphenidate, amphetamine mixed salts, or dextroamphetamine as first-line pharmacological treatment for children and adolescents diagnosed with ADHD (with or without comorbid conditions). *(Strong recommendation)*
   b) Clinicians, patients, parents and/or caregivers should collaboratively select first-line pharmacological treatment based on preferences, side effects and potential harms, pharmacokinetics (rapidity of onset, duration of action), cost, and formulary availability. *(Strong recommendation)*

9. Clinicians may recommend additional educational services offered outside of KP, such as through the school system, for children and adolescents diagnosed with ADHD. *(Weak recommendation)*

10. Cognitive behavioral therapy (CBT), family therapy, parent training, and social skills training are options for children or adolescents diagnosed with ADHD, with or without comorbidities, for whom drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy. *(Weak recommendation)*

11. For children and adolescents who are responding adequately to medication management, clinicians should not routinely add a clinic-based, non-drug intervention* for treating ADHD. *(Weak recommendation)*

12. Clinicians should not recommend dietary modifications and/or elimination diets† for the treatment of ADHD. *(Weak recommendation)*

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* Examples of clinic-based, non-drug interventions are CBT, family therapy, and parent and social skills training.
† Elimination diets were introduced with the ‘Feingold theory’ and implicated artificial colorings, preservatives and cross-reacting natural salicylates in a variety of illnesses, including ADHD (BF Feingold, Why Your Child is Hyperactive, 1974).
13. Second-line pharmacological treatment options
   a) After assessing for and addressing medication adherence and other conditions that might interfere with response, if not otherwise contraindicated, clinicians may recommend a different stimulant medication (in the same or different class) for patients who fail to adequately respond to or are intolerant of the initial stimulant. 
   (Weak recommendation)
   b) If two or more first-line stimulant formulations are contraindicated, not tolerated, or ineffective, treatment options include:
      1. Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion,
      2. Stimulant treatment augmented with guanfacine or clonidine,
      3. Guanfacine or clonidine monotherapy.
      4. Atomoxetine (KP non-formulary medication),
   (Weak recommendation)

14. Clinical follow-up for children and adolescents with ADHD who start pharmacologic treatment
   a) Clinicians should recommend one in-person office visit with a practitioner with prescriptive authority for children and adolescents during the 30-day initiation phase of drug treatment for ADHD.
   b) Clinicians should recommend a minimum of two follow-up visits within 9 months after the 30-day initiation phase visit for children and adolescents continuing drug treatment for ADHD. One of the visits may be a telephone visit with a practitioner. More frequent follow-up visits may be conducted on a case-by-case basis.
   c) At all follow-up visits, clinicians should assess patients for adverse effects, adherence to treatment, and response to treatment. Clinicians should monitor for changes in core symptoms of ADHD (hyperactivity, impulsivity, and inattention), educational function, psychosocial function, and potential side effects, such as headaches, abdominal pain, and changes in height, weight, blood pressure, pulse, or eating and sleeping patterns.
   (Weak recommendations)
15. Monitoring for adverse events
   a) Clinicians should instruct patients, parents, and/or other caregivers about cardiovascular signs and symptoms (for any stimulant), or liver dysfunction, and suicidality (for atomoxetine). Patients, parents, or caregivers should seek medical attention should any of these signs and symptoms occur. *(Strong recommendation)*
   b) Clinicians may order liver function tests for patients prescribed atomoxetine. *(Weak recommendation)*

16. Clinicians should not routinely recommend drug holidays for children and adolescents with ADHD. However, clinicians should consider the viewpoints of the patients, parents and/or other caregivers to identify the best pattern of use, which may include periods without drug treatment. *(Weak recommendation)*

17. Clinicians should assess the continuing benefit and potential risk of pharmacological treatment at least every six months. *(Weak recommendation)*

18. If the benefits continue to outweigh the risks, clinicians should prescribe pharmacological treatment for ADHD for as long as it remains clinically effective. *(Weak recommendation)*

19. Clinicians may refer children and adolescents with ADHD and common comorbid conditions (e.g., oppositional defiant, conduct, anxiety, and tic disorders) for consultation with a specialist (e.g., a child psychiatrist, behavioral health specialist, behavioral pediatrician, or ADHD champion). *(Weak recommendation)*
Rationale Decision Table

To achieve consistency with evidence quality assessments contained in the guidelines reviewed in the AGREE process, and meet the standards of the KP National Guidelines Program, the GDT translated evidence appraisal language into terms consistent with GRADE terminology. *

To determine the overall strength of the recommendations, the GDT assigned equal weight to the four GRADE domains (for details, see the rationale decision table below). For example, when less uncertainty (in balance of harms to risks, differences in values and preferences, and net benefits and costs) and higher quality evidence were identified in three or four of the four domains, the GDT assigned a strong recommendation. Otherwise, the GDT assigned a weak recommendation when uncertainty was greater in balance of harms to risks, patient values and preferences, and costs/resource implications. When the quality of evidence was very low, the GDT considered the recommendation as weak (regardless of the weight of the other four domains).

# ADHD Rationale Decision Table

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Recommendation</th>
<th>Basis of Recommendation†‡</th>
<th>Quality of Evidence</th>
<th>Balance of Benefits Versus Harms and Burdens</th>
<th>Values and Preferences</th>
<th>Costs and Resource Implications</th>
</tr>
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<tbody>
<tr>
<td>1. Who to screen/evaluate for ADHD</td>
<td>Clinicians should not universally screen children and adolescents for ADHD. (&lt;strong&gt;Strong recommendation&lt;/strong&gt;)</td>
<td>&lt;strong&gt;Strong&lt;/strong&gt;: less uncertainty in 3 of 4 domains.</td>
<td>Moderate-low: NICEʻ(1) appraised the Quality of Evidence as moderate (given that one study was included in the assessment (p. 211), while SIGN’s(2) screening recommendation is based on expert opinion (p. 7)). Based on the results of an RCT (screening vs. no screening), NICEʻ(1) determined there is no evidence to indicate that universal screening has beneficial effects on ADHD core symptoms and conduct problems.</td>
<td>There are substantial functional and educational benefits of screening children and adolescents suspected of having ADHD and low risk of serious harms. The NICEʻ(1) guideline (p. 224) reports there is no evidence to indicate that universal screening has beneficial effects on ADHD core symptoms and conduct problems. Once identified, children and adolescents suspected of having ADHD should receive the appropriate referrals and/or support at the earliest stage possible.</td>
<td>The GDT believes that caregivers and patients would generally weigh the benefits of appropriate diagnosis and treatment in children and adolescents suspected of having ADHD as greater than the risks (e.g., potential for false positives, time required for a formal evaluation) associated with screening and universal screening. Variation in patient acceptance of ADHD evaluation for children and adolescents with signs, symptoms, or impairments suggestive of ADHD is likely to be low.</td>
<td>Low</td>
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<td>2. Clinicians should evaluate children and adolescents for ADHD when they have signs, symptoms, or impairment suggestive of ADHD. (&lt;strong&gt;Strong recommendation&lt;/strong&gt;)</td>
<td>Clinicians should evaluate children and adolescents for ADHD when they have signs, symptoms, or impairment suggestive of ADHD. (&lt;strong&gt;Strong recommendation&lt;/strong&gt;)</td>
<td>Strong: less uncertainty in 3 of 4 domains.</td>
<td>Evidence: moderate-low quality</td>
<td>Balance of Benefits to Harms: low uncertainty</td>
<td>Values and Preferences: low uncertainty</td>
<td>Costs: low uncertainty</td>
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†‡ Justification for recommendation strength (i.e., strong or weak), given the relative weight ascribed to four GRADE domains (quality of evidence, balance of benefits to harms, values and preferences, and costs and resource implications).
### Clinical Question
3. As part of the evaluation and diagnosis of ADHD in children and adolescents, clinicians should use structured, validated rating scales§§, and refer to and follow the DSM-5 diagnostic criteria. *(Strong recommendation)*

### Basis of Recommendation

#### Strong: less uncertainty in 3 of 4 domains.
1. **Evidence:** high quality
2. **Balance of Benefits to Harms:** low uncertainty
3. **Values and Preferences:** low uncertainty
4. **Costs:** low uncertainty

### Quality of Evidence
High: The recommended diagnostic criteria and tools are well validated, as noted in the 2009 KP(3) guideline (p. 12).

### Balance of Benefits Versus Harms and Burdens
The use of DSM-5 criteria and other validated tools for the evaluation and diagnosis of ADHD in children and adolescents renders benefits (e.g., accurate diagnoses), with low risk of harm.

### Values and Preferences
The GDT believes that variation in caregiver or patient acceptance of the type of diagnostic criteria and evaluation used for ADHD evaluation is likely to be low.

### Costs and Resource Implications
Low

§§ The publicly available Vanderbilt ADHD Rating Scales are recommended as part of the evaluation and diagnosis of ADHD in children and adolescents. The following behavioral rating scales are options to be used in addition to the initial evaluation: Conners’ Rating Scales (the revised Conners’ Parent Rating Scale (CPRS-R), the revised Conners’ Teacher Rating Scale (CTRS-R), and the Conners'/Wells Self-Report of Symptoms rating scale (CASS)), Achenbach Scales: CBCL, TRF, YSR, ADHD Rating Scale – IV (ADHD RS-IV) (DSM-5-based), Swan, Nolan, and Pelham Questionnaire (SNAP) (DSM-5-based), and Achenbach and Vanderbilt behavioral rating scales can be utilized to assess some comorbid disorders.
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<td>3. Baseline assessments</td>
<td>4. Clinicians should conduct a baseline physical assessment (including measurement of pulse, blood pressure, weight and height with the appropriate use of percentile charts) prior to initiating pharmacological therapy. (Strong recommendation)</td>
<td>(4): Strong: less uncertainty in 3 of 4 domains. 1. Evidence: insufficient †† †† 2. Balance of Benefits to Harms: low uncertainty 3. Values and Preferences: low uncertainty 4. Costs: low uncertainty</td>
<td>(4): None/ insufficient evidence</td>
<td>(4): Benefits incurred from obtaining patient baseline information prior to initiating pharmacological therapy for ADHD outweigh the risks. The GDT agrees that such an assessment will yield important information that could affect or change the choice or course of treatment. The SIGN(^2) guideline suggests that, prior to the initiation of pharmacological therapy, a baseline assessment is undertaken, including as a minimum, pulse measurement, blood pressure, weight and height with the appropriate use of percentile charts in all measured parameters (p. 14). The NICE(^1) guideline notes that baseline physical assessments can help rule out undiagnosed disorders with symptoms that in rare instances may mimic or cause some aspects of ADHD, such as hearing impairment, epilepsy, thyroid disorder and iron deficiency anemia. There may also be other coexisting physical, neurological and developmental disorders that should be identified (including dyspraxia, chronic tic disorders or Tourette’s syndrome, and sleep disorders) which will then shape later management (p. 25). The guideline also suggests that if ADHD is diagnosed and drug therapy is considered, monitoring of height and weight, blood pressure, and pulse rate should be continued.</td>
<td>(4): The GDT believes that variation in patient, parent and/or caregiver acceptance of conducting a baseline physical assessment is likely to be low.</td>
<td>(4): Low</td>
</tr>
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</table>

*** Justification for recommendation strength (i.e., strong or weak), given the relative weight ascribed to four GRADE domains (quality of evidence, balance of benefits to harms, values and preferences, and costs and resource implications).

†† †† Despite the lack of evidence, the GDT agree that baseline physical assessments completed prior to the initiation of pharmacologic treatment are the current practice of care.
### Clinical Question 5
Clinicians may recommend cardiac risk evaluation or consultations prior to prescribing psychostimulants for children and adolescents with ADHD with known cardiac abnormalities. *(Weak recommendation)*

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<td>(5): Weak - very low evidence quality.</td>
<td>(5): Very Low: quality of evidence from the guidelines reviewed (2005 FDA alert on Adderall from KP[3] (p. 75) and recommendations from NICE[1] (p. 304) are based on case reports and expert opinion, while SIGN’s[2] recommendation (pgs.16 and 19) is based on Grade D evidence (extrapolate evidence)). With the addition of the AHRQ review, the quality of the evidence improves to low-moderate.</td>
<td>(5): Stimulant medication therapy for ADHD has been traditionally contraindicated in patients with known cardiac abnormalities. The GDT agrees that the risks of cardiac risk evaluation prior to initiation of psychostimulant therapy are generally low, and that children or adolescents with cardiac abnormalities have or will likely be referred to Cardiology for evaluation for reasons other than ADHD. As cardiac risk has been discussed in the literature, the NICE[1] guideline also considers the balance between desirable and undesirable effects by reporting that before drug treatment initiation, children and young people with ADHD should have a full pre-treatment assessment, which should include (but is not limited to) family history of cardiac disease and examination of the cardiovascular system as well as an electrocardiogram (ECG) if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination (p. 304).</td>
<td>(5): Variation in values and preferences regarding having a child or adolescent’s cardiac risk evaluated prior to medication initiation is likely to be low.</td>
<td>(5): Low-moderate, based upon insurance coverage of the patient/family, family financial resources and specifics of patient and family past history. The systems cost for KP may be variable, based on variation in additional workup ordered in the cardiac risk assessment.</td>
<td></td>
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</table>

| Evidence: very low | Balance of Benefits to Harms: low uncertainty | Values and Preferences: low uncertainty | Costs: moderate to low uncertainty |

NICE[1] notes that while stimulants have proven efficacy, the literature on medication has not yet shed sufficient light on risks (which include cardiac disease, psychosis and sudden death); p. 515.

SIGN[2] notes that some cases of sudden death attributed to psycho-stimulants were found in children with pre-existing cardiac risk factors or were co-prescribed other treatments. The number of reported deaths was extremely low, compared with the overall number of prescriptions prescribed (FDA, 2006). Despite the low incidence of death, the guideline developers note that sudden death attributable to psycho stimulants is under investigation.

* Justification for recommendation strength (i.e., strong or weak), given the relative weight ascribed to four GRADE domains (quality of evidence, balance of benefits to harms, values and preferences, and costs and resource implications).
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</table>
| 3. Baseline assessments (continued) | 6. Clinicians should not perform psychodiagnostic tests as part of ADHD evaluation in the absence of other indications. (Strong recommendation) | (6): Strong – less uncertainty in 3 of 4 domains.  
1. Evidence: low quality  
2. Balance of Benefits to Harms: low uncertainty  
3. Values and Preferences: low uncertainty  
4. Costs: moderate to low uncertainty | (6): Low: SIGN’s(2) recommendation is based on C grade evidence (p. 9).  
SIGN(2) identified two studies that examined research assessment methods and tests in young people with ADHD (Barkley RA et al, 1991; Goldstein et al, 1998). The results of these studies suggest that research measures or tests do not distinguish children and adolescents with ADHD from peers without ADHD.  
(6): Psychodiagnostic testing does not confer significant benefits as part of the evaluation and diagnosis of ADHD. The SIGN(2) guideline reports that while there is extensive research literature examining individual and groups of laboratory and psychodiagnostic assessment measures, in general these measures do not distinguish children and young people with ADHD/HKD from psychiatric controls or normal peers (p. 9). | (6): The GDT agrees that variation is likely to be low among patients, parents and/or caregivers for psycho-diagnostic testing. | (6): Moderate. The costs of tests are low but to administer, score, and interpret an additional battery of tests is time-consuming and would incur added costs. These costs would vary depending on the type of practitioner administering the tests. |
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<tr>
<td>3. Baseline assessments (continued)</td>
<td>7. In the absence of signs or symptoms of atopy, clinicians should not refer children and adolescents with ADHD for allergy evaluation, as it is unlikely to change the diagnosis or treatment plan.</td>
<td><em>(7): Weak – greater uncertainty in 2 of 4 domains.</em> 1. <strong>Evidence:</strong> insufficient 2. <strong>Balance of Benefits to Harms:</strong> low to moderate uncertainty 3. <strong>Values and Preferences:</strong> low uncertainty 4. <strong>Costs:</strong> low to moderate uncertainty</td>
<td><em>(7): None/insufficient evidence. The results of one RCT on the use of IgE blood tests to identify food sensitivities found that the underlying mechanism of food sensitivity in ADHD could be non-allergic (due to raised IgE levels in a few of 100 children).</em></td>
<td><em>(7): In the absence of atopy signs or symptoms, allergy evaluation and/or referral does not confer known benefits to children or adolescents with ADHD. Allergy testing does incur some risk.</em></td>
<td><em>(7): In the absence of any evidence of benefit, patients, parents and/or other caregivers are likely to agree that such evaluations are not needed.</em></td>
<td><em>(7): Low-moderate, based upon insurance coverage of the patient, parent, and/or other caregiver.</em></td>
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<td>Clinical Question</td>
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<td>Basis of Recommendation</td>
<td>Quality of Evidence</td>
<td>Balance of Benefits Versus Harms and Burdens</td>
<td>Values and Preferences</td>
<td>Costs and Resource Implications</td>
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<td>4. First-line Pharmacologic Treatment Options</td>
<td>8. First-line pharmacological treatment</td>
<td>(8a): Strong – less uncertainty in 3 of 4 domains.</td>
<td>(8a): Moderate: The KP (3) guideline lists the evidence as grade B (p. 28) while NICE (1) rates the evidence for methylphenidate and atomoxetine as high to moderate (pgs 254-258). Based on moderate evidence, KP (3) recommends methylphenidate, amphetamine mixed salts, and dextroamphetamine as first-line treatment for ADHD. NICE (1) found that methylphenidate and atomoxetine are the only drugs where clear RCT evidence exists for clinical effectiveness in reducing ADHD symptoms in school-age children and young people (high to moderate evidence). When compared with placebo, the size of clinical effect is largest for methylphenidate. For children, NICE (1) found no trials on dextroamphetamine that met the quality criteria and therefore had no evidence on its efficacy.</td>
<td>(8a): KP notes good evidence that methylphenidate and fair evidence that dexamphetamine, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil are efficacious in reducing core symptoms of ADHD and, in some cases, other measures of educational and psychosocial function. Although there is fair evidence that adverse events do occur in children and adolescents with all of these drugs, with the exception of modafinil, the proven benefits were determined to outweigh the risk of harm for routine use (p. 7).</td>
<td>(8a): The GDT believes that there may be variation in caregiver or patient acceptance of first-line medication because of tolerability issues with stimulants.</td>
<td>(8a): Low (for generic stimulants)</td>
</tr>
<tr>
<td></td>
<td>a) Clinicians should recommend stimulant medications methylphenidate, amphetamine mixed salts, and dextroamphetamine as first-line treatment for children and adolescents diagnosed with ADHD (with or without comorbid conditions). (Strong recommendation)</td>
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National ADHD Clinical Practice Guideline
### Clinical Question

**b)** Clinicians, patients, parents and/or caregivers should collaboratively select first-line pharmacological treatment based on preferences, side effects and potential harms, pharmacokinetics (rapidity of onset, duration of action), cost, and formulary availability (*Strong recommendation*)

#### Basis of Recommendation

**b**: Strong – less uncertainty in 3 of 4 domains.

1. **Evidence**: very low
2. **Balance of Benefits to Harms**: low uncertainty
3. **Values and Preferences**: low uncertainty
4. **Costs**: low uncertainty

#### Quality of Evidence

**b**: Very Low. The KP\(^{(3)}\) guideline labels the evidence as insufficient (p. 28). There is a lack of evidence on a clearly superior stimulant medication.

This appraisal takes into account the differences in medications and preferred formularies between the US and UK.

#### Balance of Benefits Versus Harms and Burdens

**b**: Given the lack of evidence on a clearly superior stimulant medication, the GDT agrees that when choosing a first-line treatment, decisions should be based on clinician and parent preferences, side effects, pharmacokinetics, cost, and formulary availability (KP\(^{(3)}\) guideline, p. 7). This shared decision-making approach will also prove beneficial when informing the patient and caregiver of potential side effects and harms associated with stimulant treatment.

#### Values and Preferences

**b**: The GDT believes that variation in caregiver or patient acceptance of shared decision-making approach in selecting among first-line stimulant preparations is likely to be low.

#### Costs and Resource Implications

**b**: Low
### Clinical Question

**5. Non-pharmacologic Treatment Options**

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<th>Values and Preferences</th>
<th>Costs and Resource Implications</th>
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<tbody>
<tr>
<td>9.</td>
<td>Clinicians may recommend additional educational services offered outside of KP, such as through the school system, for children and adolescents diagnosed with ADHD. <em>(Weak recommendation)</em></td>
<td><em>(9): Weak – very low quality of evidence and greater uncertainty in 2 of 4 domains.</em></td>
<td><em>(9): Very Low: The KP recommendations are based on expert opinion (recommendation 10, p. 81; recommendation 12, p. 11).</em></td>
<td><em>(9): The potential benefits conferred to a child or adolescent with ADHD seeking educational services offered outside KP (e.g., in a school setting) would likely outweigh serious harm. The GDT agrees that supplemental services may augment clinic-based treatment and help address educational or psychosocial issues observed in children or adolescents diagnosed with ADHD. The GDT acknowledges the difficulty patients may experience accessing such services, especially if offered through the public school system (given the variability of available resources across different school systems and the difficulties of assessing the quality and consistency of such services).</em></td>
<td><em>(9): The GDT believes that there is likely to be moderate variation in patient and caregiver acceptance of seeking and desire to seek additional educational resources outside KP.</em></td>
<td><em>(9): Varies, depending on type of educational facility (e.g., public versus private facility). The KP guideline notes these services as offered and paid for outside of KP (p. 93).</em></td>
</tr>
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National ADHD Clinical Practice Guideline
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<tr>
<td>5. Non-pharmacologic Treatment Options (continued)</td>
<td>10. Cognitive behavioral therapy (CBT), family therapy, parent training, and social skills training are options for children or adolescents diagnosed with ADHD, with or without comorbidities, for whom drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy. <em>(Weak recommendation)</em></td>
<td><em>(10): Weak – very low quality of evidence and greater uncertainty in 2 of 4 domains.</em></td>
<td><em>(10): Very Low. The KP recommendations are based on expert opinion (recommendation 10, p. 81; recommendation 12, p. 11).</em></td>
<td><em>(10): The potential benefits conferred to a child or adolescent with ADHD seeking clinic-based non-drug interventions (e.g., behavioral therapy/cognitive behavioral therapy (CBT), family therapy, parent training, and social skills training) when medication treatment is contraindicated, not tolerated, or not desired would likely outweigh risk of harm. The GDT agrees that the use of those clinic-based, non drug interventions would likely those children or adolescents with ADHD unable to benefit from pharmacologic therapy. Harm could be incurred by patients and families seeking interventions (e.g., from the internet) whose effectiveness has not been rigorously evaluated. The previous KP(3) guideline found that given the limited evidence available directly comparing non-drug interventions with drug treatment, drug treatment appears to be more favorable over non-drug interventions. However, clinic-based non-drug interventions are options for children or adolescents for whom drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy (p. 92).</em></td>
<td><em>(10): The GDT believes that variation in patient and caregiver acceptance of considering clinic-based, non-drug interventions when medication treatment is not an option is likely to be low.</em></td>
<td><em>(10): Low-moderate for the patient, based on the insurance coverage of the patient/family and intervention chosen.</em></td>
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<tr>
<td>5. Non-pharmacologic Treatment Options (continued)</td>
<td>11. For children and adolescents who are responding adequately to medication management, clinicians should not routinely add a clinic-based, non-drug intervention (e.g., CBT, parent or skills training) for treating ADHD (Weak recommendation)</td>
<td>(11): <strong>Weak</strong> – very low quality of evidence and greater uncertainty in 2 of 4 domains. 1. Evidence: very low 2. Balance of Benefits to Harms: low uncertainty 3. Values and Preferences: low to moderate uncertainty 4. Costs: low to moderate uncertainty</td>
<td>(11): Very low. The KP&lt;sup&gt;(3)&lt;/sup&gt; recommendation was based on expert opinion (p. 81).</td>
<td>(11): When children and adolescents are responding well to medication management, the GDT agrees that the addition of clinic-based non-drug interventions for treating the core symptoms of ADHD will not yield significant benefits. The KP&lt;sup&gt;(3)&lt;/sup&gt; guideline notes that the potential harms and costs of routinely adding non-drug interventions to successful drug treatment outweigh any potential, but still unknown, benefits (p. 97).</td>
<td>(11): Given that patients and/or caregivers may be interested in exploring non-medication treatment pathways, variation in patient and caregiver acceptance of this recommendation may be low to moderate.</td>
<td>(11): Low-moderate, based on the insurance coverage of the patient, parent and/or other caregiver and intervention chosen.</td>
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<tr>
<td>5. Non-pharmacologic Treatment Options (continued)</td>
<td>12. Clinicians should not recommend dietary modifications and/or elimination diets* for the treatment of ADHD.</td>
<td><strong>(12): Weak</strong> – greater uncertainty in 2 of 4 domains.</td>
<td><strong>(12): Low.</strong> NICE&lt;sup&gt;(1)&lt;/sup&gt; (pgs. 29, 112, 139) and SIGN&lt;sup&gt;(2)&lt;/sup&gt; (p. 23) recommendations, as well as the FDA position statement (see Appendix B), are based on small studies.</td>
<td><strong>(12): In the absence of other indications, dietary supplements and modifications (e.g., elimination diets) do not confer known or proven benefits to children or adolescents with ADHD. Unnecessary use of supplements or elimination diets can result in inconvenience for families, and unwarranted use of some supplements could expose patients to a risk of unnecessary side effects. The harms may therefore outweigh the benefits.</strong> The NICE&lt;sup&gt;(1)&lt;/sup&gt; guideline notes that elimination diets are potentially difficult for families to manage, and might lead to unbalanced diet and nutritional problems, all issues not satisfactorily addressed by trials (p. 228). The SIGN&lt;sup&gt;(2)&lt;/sup&gt; guideline adds that avoiding foods and drinks that contain certain artificial colors and/or preservatives may help some children with ADHD. Parents should be advised to take reasonable steps to limit the number and variety of these in their children's diets, excluding any item that seems to provoke an extreme physical or behavioral reaction (p. 23).</td>
<td><strong>(12): The GDT believes that there may be variation in patient acceptance of a recommendation against dietary modifications or supplements (in the absence of other indications) due to personal beliefs, personal anecdote, anecdotal experiences of friends, or misinformation or inaccurate information proliferated on the internet and in the lay media.</strong></td>
<td><strong>(12): Low-moderate, based on the insurance coverage of the patient, parent and/or other caregiver and intervention chosen.</strong></td>
</tr>
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* Elimination diets were introduced with the ‘Feingold theory’ and implicated artificial colorings, preservatives and cross-reacting natural salicylates in a variety of illnesses, including ADHD (BF Feingold, *Why Your Child is Hyperactive*, 1974).
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<tbody>
<tr>
<td>6. Second-line Pharmacologic Treatment Options</td>
<td>13. Second-line pharmacological treatment options</td>
<td>Weak – greater uncertainty in 2 of 4 domains.</td>
<td>Moderate-Low: KP(^3) guideline labels evidence as Grade C/Insufficient (p. 8, 99).</td>
<td>Unless contraindicated, the benefits conferred by prescribing a different first-line medication (i.e., replacing one first-line medication with another) would likely outweigh the harms when patients are unresponsive to or are intolerant to the initial first-line medication. The GDT agrees that the benefits of stimulants for the treatment of ADHD are well-documented and the use of a different stimulant (in the same or different class) might well provide benefit to patients unresponsive to first. There is no evidence to suggest a preferred order for trial of first-line medications.</td>
<td>The GDT believes that variation in patient and caregiver acceptance of the recommended second-line treatment options, including consultation is likely to be low-moderate.</td>
<td>Low - For substitution of one formulary stimulant for another to moderate (for combined drug treatment, use of second-line medication options), or added costs due to additional referral.</td>
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Continued on next page.

KP\(^3\) notes fair evidence that atomoxetine is efficacious in reducing core symptoms of ADHD. Long-term placebo-controlled or open-label follow-up studies demonstrating efficacy or overall safety have not been conducted on atomoxetine in children or adolescents with ADHD. Therefore, atomoxetine is included as the second-line treatment option.

NICE\(^1\) reports limited evidence that the off-label use of modafinil (high to moderate evidence quality), clonidine (moderate evidence, due to paucity of studies for children) and bupropion (which offered no statistically significant evidence for reductions in ADHD core symptoms or behavior in children with ADHD) reduces symptoms of ADHD in children (and adults for bupropion). However, NICE\(^1\) found these drugs produce more adverse effects than placebo (p. 291).
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<td></td>
<td>b) If two or more first-line stimulant formulations are contraindicated, not tolerated, or ineffective, treatment options include:</td>
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<td>1. Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion</td>
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<td>2. Stimulant treatment augmented with guanfacine or clonidine</td>
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<td>3. Guanfacine or clonidine monotherapy</td>
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<td>4. Atomoxetine (KP non-formulary medication)</td>
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<td></td>
<td><em>(Weak recommendation)</em></td>
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<tr>
<td>7. Monitoring of ADHD Medication use</td>
<td>14. Clinical follow-up for children and adolescents with ADHD who start pharmacologic treatment</td>
<td>(14 a-c): Weak – Recommendations 14a and 14b reflect the 2009 HEDIS measures for monitoring of ADHD medication use in children. The GDT agreed that adolescents should also be monitored in accordance with 14a and 14b. While the recommendations are based on HEDIS standards, the quality of evidence is very low. Continued on next page</td>
<td>(14 a-c): Very Low: The KP (3) recommendation is based on HEDIS measures (for recommendations 14a and 14b) while SIGN is based on expert opinion (p. 39). Recommendation 14c is based on expert opinion and not specifically addressed in the 2009 HEDIS measure.</td>
<td>(14 a-c): In patients on stimulant therapy, ongoing follow-up affords the clinician an opportunity to gauge adverse events, treatment adherence, and response to treatment with low risk of harm. Despite the lack of evidence on an optimal follow-up interval, the KP ADHD guideline recommends following the current 2009 HEDIS standard to support the organization's quality and accreditation initiatives related to the monitoring of ADHD medications (p. 110).</td>
<td>(14 a-c): The GDT believes that variation in patient and caregiver acceptance of recommended monitoring intervals is likely to be low.</td>
<td>(14 a-c): Low to moderate</td>
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<tr>
<td>c) At all follow-up visits, clinicians should assess patients for adverse effects, adherence to treatment, and response to treatment. Clinicians should monitor for changes in core symptoms of ADHD (hyperactivity, impulsivity, and inattention), educational function, psychosocial function, and potential side effects, such as headaches, abdominal pain, and changes in height, weight, blood pressure, pulse, or eating and sleeping patterns. (Weak recommendations)</td>
<td>Recommendation 14c is not specifically addressed in the 2009 HEDIS standard and is based on expert opinion (and the quality of evidence is thus very low).</td>
<td>Evidence: very low</td>
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<td></td>
<td>1. Evidence: very low</td>
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<td>2. Balance of Benefits to Harms: low uncertainty</td>
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<td>3. Values and Preferences: low uncertainty</td>
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<td>4. Costs: low to moderate uncertainty</td>
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**Quality of Evidence**

- Evidence: very low
- Balance of Benefits to Harms: low uncertainty
- Values and Preferences: low uncertainty
- Costs: low to moderate uncertainty
### Clinical Question

7. Monitoring of ADHD Medication use (continued)

### Recommendation

15. Monitoring for adverse events

- a) Clinicians should instruct patients, parents, and/or other caregivers about cardiovascular signs and symptoms (for any stimulant), or liver dysfunction, and suicidality (for atomoxetine). Patients, parents, or caregivers should seek medical attention should any of these signs and symptoms occur.  
  
  *(Strong recommendation)*

- b) Clinicians may order liver function tests for patients prescribed atomoxetine.

  *(Weak recommendation)*

### Basis of Recommendation

15: Strong – less uncertainty in 3 of 4 domains.

1. **Evidence:** moderate
2. **Balance of Benefits to Harms:** low uncertainty
3. **Values and Preferences:** low uncertainty
4. **Costs:** low uncertainty

### Quality of Evidence

15: Moderate: The KP(3) recommendations are based on FDA medication advisory, RCTs, and case reports; NICE(1) appraises the evidence as moderate (beginning p. 233).

Given the warnings issued by the FDA (beginning in 2005) on hepatoxicity and suicidality from atomoxetine, KP(3) recommends that patients and caregivers recognize signs/symptoms of liver dysfunction, cardiovascular and psychiatric adverse events.

Based on known adverse events associated with atomoxetine (Wolraich(4) et al, 2007), NICE(1) reports that parents or caregivers should also be warned about the rare potential for liver damage in rare cases with atomoxetine (usually presenting as abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice), p.258.

### Balance of Benefits Versus Harms and Burdens

15: There are potentially significant benefits in advising patients and caregivers to recognize signs and symptoms of adverse events associated with stimulant treatment, with low risk of harm.

### Values and Preferences

(15a): The GDT believes that patients and caregivers would weigh the benefits of recognizing a serious adverse event in a child or adolescent receiving stimulant therapy as greater than any potential harm. Thus, variation in patient and caregiver acceptance of monitoring for adverse events such as cardiovascular events, hepatoxicity, and suicidality is likely to be low.

### Costs and Resource Implications

(15a): Low
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<th>Costs and Resource Implications</th>
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<tr>
<td>8. Drug Holidays</td>
<td>16. Clinicians should not routinely recommend drug holidays for children and adolescents with ADHD. However, clinicians should consider the viewpoints of the patients, parents and/or other caregivers to identify the best pattern of use, which may include periods without drug treatment. <em>(Weak recommendation)</em></td>
<td>16). Weak – very low evidence quality and greater uncertainty in 2 of 4 domains. 1. <strong>Evidence</strong>: very low 2. <strong>Balance of Benefits to Harms</strong>: low to moderate uncertainty 3. <strong>Values and Preferences</strong>: significant (moderate to high) uncertainty 4. <strong>Costs</strong>: low uncertainty</td>
<td>16). Very Low: NICE(^1) recommendation is based on expert opinion (p. 314).</td>
<td>16). As ADHD medication should be continued as long as effective and drug holidays have not been shown to be generally beneficial, risks associated with medication cessation or drug holiday might outweigh the benefits. The NICE(^1) guideline notes that while drug holidays are not routinely recommended, consideration should be given to the parent or caregiver and child or young person with ADHD working with their healthcare professional to find the best pattern of use, which may include periods without drug treatment (p. 276).</td>
<td>16). While the GDT does not recommend drug holidays, the team believes that consideration should be given to identifying the best pattern of use, which may include periods without treatment. As a result, variation in patient and caregiver preferences may be significant.</td>
<td>16). Low</td>
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<td>9. Duration of Medication Treatment</td>
<td>17. Clinicians should assess the continuing benefit and potential risk of pharmacological treatment at least every six months. (Weak recommendation)</td>
<td>(17, 18): Weak – very low quality of evidence.</td>
<td>(17, 18): Very Low: The SIGN(^2) recommendation is a good practice point, based on expert opinion (p. 14).</td>
<td>(17, 18): The GDT agrees that benefits incurred from conducting routine assessments on medication need and continuation would far outweigh risks. The SIGN(^2) guideline notes that the continuing benefit from and need for medication should be assessed at least once per year (p. 14).</td>
<td>(17, 18): Variation in patient and caregiver preferences for routine medication assessments is likely to be low.</td>
<td>(17, 18): Low</td>
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<td></td>
<td>18. If the benefits continue to outweigh the risks, clinicians should prescribe pharmacological treatment for ADHD for as long as it remains clinically effective. (Weak recommendation)</td>
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Quality of Evidence:
- **Very Low:** The SIGN\(^2\) recommendation is a good practice point, based on expert opinion (p. 14).
- **Weak:** The NICE\(^1\) guideline developers note limited empirical evidence is available to guide clinicians on the optimum duration of treatment and when to consider drug discontinuation. However, NICE\(^1\) suggests that for people taking methylphenidate, atomoxetine or dexamphetamine, height should be measured every 6 months in children and young people and weight should be measured 3 and 6 months after drug treatment has stated and every 6 months thereafter in children and young people (pgs. 311 and 377).

Balance of Benefits Versus Harms:
- The GDT agrees that benefits incurred from conducting routine assessments on medication need and continuation would far outweigh risks. The SIGN\(^2\) guideline notes that the continuing benefit from and need for medication should be assessed at least once per year (p. 14).

Values and Preferences:
- Variation in patient and caregiver preferences for routine medication assessments is likely to be low.

Costs and Resource Implications:
- Low.
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<tr>
<td>10. ADHD and Referral for Comorbidities</td>
<td>19. Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion is an option for children or adolescents with common comorbid conditions such as oppositional defiant disorder and conduct, anxiety, and tic disorders. (Weak recommendation)</td>
<td>Weak – very low quality of evidence. 1. Evidence: very low 2. Balance of Benefits to Harms: low uncertainty 3. Values and Preferences: low uncertainty 4. Costs: low to moderate uncertainty</td>
<td>Very Low: The KP(^{(3)}) and SIGN(^{(2)}) recommendations are based on expert opinion (KP, pgs. 22, 99 and SIGN p. 7, 9, 27).</td>
<td>Benefits are expected when a child or adolescent with ADHD and a concomitant comorbidity are referred to specialty care or others expert in ADHD treatment, given the complexities of comorbidity. The KP guideline notes that in cases where improvements in ADHD symptoms are not seen in children or adolescents with comorbid conditions after first-line and second-line treatment has been tried, a referral to a subspecialist (e.g., child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion) for more treatment options is recommended (p. 100).</td>
<td>The GDT believes that patients would generally weigh the potential benefits of referral or consultation to a specialist greater than the costs or risk of not seeking referral and/or treatment when a child or adolescent with ADHD presents with comorbidity. Any variation in patient and caregiver acceptance is likely to be low.</td>
<td>Low-moderate, based upon the insurance coverage of the patient/family.</td>
</tr>
</tbody>
</table>
Appendix A: Criteria for Grading the Evidence

GRADE System of Evidence Rating

The overall quality of evidence for outcomes was assessed using a method developed by the GRADE Working Group, which classified the grade of evidence across outcomes according to the following criteria:

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

GRADE also suggests using the following scheme for assigning the “grade” or strength of evidence:

**Criteria for Assigning Grade of Evidence**\(^{(5, 6)}\)

**Type of evidence**
- Randomized trial = high
- Observational study = low
- Any other evidence = very low

**Decrease grade if:**
- Serious (-1) or very serious (-2) limitation to study quality
- Important inconsistency (-1)
- Some (-1) or major (-2) uncertainty about directness
- Imprecise or sparse data (-1)
- High probability of reporting bias (-1)

**Increase grade if:**
- Strong evidence of association – significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association – significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

* National Institute for Health and Clinical Excellence (NICE) Guideline uses the GRADE system of evidence rating \((p. 54)\).
Determinants of the Recommendation Strength<sup>5·7</sup>

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance between desirable and undesirable effects</td>
<td>The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted.</td>
</tr>
<tr>
<td>Quality of evidence</td>
<td>The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted.</td>
</tr>
<tr>
<td>Values and preferences</td>
<td>The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted.</td>
</tr>
<tr>
<td>Costs (resource allocation)</td>
<td>The higher the costs of an intervention — that is, the greater the resources consumed — the lower the likelihood that a strong recommendation is warranted.</td>
</tr>
</tbody>
</table>
Scottish Intercollegiate Guidelines Network (SIGN)

<table>
<thead>
<tr>
<th>LEVELS OF EVIDENCE</th>
<th>GRADES OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
<td>At least one meta-analysis, systematic review, or RCT rated &lt;=1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated &lt;=1-, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2--</td>
</tr>
<tr>
<td>1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2-</td>
</tr>
<tr>
<td>2++ High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2-</td>
</tr>
<tr>
<td>2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
<td></td>
</tr>
<tr>
<td>2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
<td></td>
</tr>
<tr>
<td>3 On-analytic studies, e.g., case reports, case series</td>
<td></td>
</tr>
<tr>
<td>4 Expert opinion</td>
<td></td>
</tr>
</tbody>
</table>

**GOOD PRACTICE POINTS**

0 Recommended best practice based on the clinical experience of the guideline development group.
Appendix B: Search Strategy, Evidence, and Supporting Documentation

Search Strategy *

A comprehensive literature search was performed in March to April 2011 to identify rigorous external ADHD guidelines for children and adolescents. The Guidelines International Network (GIN) and Turning Research Into Practice (TRIP) databases were searched for full guidelines relating to ADHD in individuals ages 6 to 18 years. The inclusion criteria were full guidelines in English on children and adolescents, which were published from 2007 through the present. Of the 11 guidelines preliminarily identified as meeting the search parameters, four did not meet the preliminary inclusion criteria.

Considered to be a position statement with a narrow focus on one first-line ADHD treatment, the guideline published by the Canadian Pediatric Society was excluded. Three additional guidelines - SCHIN (2010), National Health and Medical Research Council (2009), and National Health and Medical Research Council (2011) - were also excluded. While only the draft version of the National Health and Medical Research Council (2009) could be located, its 2011 version is currently in development.

Three remaining full guidelines developed by the National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), and American Academy of Child and Adolescent Psychiatry (AACAP) were assessed, first for rigor of development. After evaluating the level of rigor, three assessors determined that two of the three guidelines were rigorous enough to proceed with the rest of the AGREE II evaluation.

Both guidelines (NICE\(^1\) and SIGN\(^2\)) were deemed acceptable after the three raters assessed the remaining domains: scope and purpose, stakeholder involvement, clarity of presentation, applicability, and editorial independence. The current KP guideline was accepted by the GDT as a foundation for the update, and was not appraised using AGREE II.

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* Search and data extraction performed by outside vendor Doctor Evidence: www.doctorevidence.com
## Search Results

<table>
<thead>
<tr>
<th>Database</th>
<th>Terms</th>
<th>Type and Limits</th>
<th>Time Frame</th>
<th># Found</th>
<th># Rigorous External Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIN, TRIP Database (AHRQ, Bandolier, New Zealand Guideline Group, Monash University Evidence Centre Reports, NICE, SCHIN)</td>
<td>ADHD / ADHD in children and young people / Attention Deficit Hyperactivity Disorder / Attention Deficit Hyperactivity Disorder in children and adolescents / Attention Deficit Hyperactivity Disorder in children and young people</td>
<td>Full Guideline, English language</td>
<td>2007 to present</td>
<td>11</td>
<td>2</td>
</tr>
</tbody>
</table>
The following Quorum flowchart describes the guideline selection process outlined above. The clinical lead, methodologist, and evidence analyst examined eleven guidelines. From these, two full external guidelines were chosen.

**2012 KP ADHD Guideline Inclusion/Exclusion Quorum Diagram**

- **Potential Guidelines found** 
  \( (n = 11) \)
  - Rejected - did NOT meet Preliminary Inclusion Criteria \( (n = 4) \)
  - Remaining Guidelines reviewed \( (n = 7) \)
    - Rejected - Position statement / scope too narrow \( (n = 1) \)
    - Potentially Acceptable Guidelines \( (n = 6) \)
      - Existing guideline not found or guideline only available in draft (not finalized) \( (n = 3) \)
      - Lead Group conducted AGREE II Rigor Assessment \( (n = 3) \)
        - Guidelines did not meet minimum level of Rigor \( (n = 1) \)
      - Lead Group conducted full AGREE II assessment for rigorous guidelines \( (n = 2) \)
        - Poor overall quality \( (n = 0) \)
  - Final Selection of ADHD Clinical Practice Guidelines \( (n = 2) \)
Evidence and Supporting Documentation

1. Who to Screen/Evaluate for ADHD

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>1) Which children and adolescents should be screened/evaluated for ADHD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children and adolescents (aged 6 to 18 years) without a diagnosis of ADHD and who do not have any of the following:</td>
</tr>
<tr>
<td></td>
<td>Mental retardation (or low IQ, &lt; 80)</td>
</tr>
<tr>
<td></td>
<td>Pervasive developmental disorder</td>
</tr>
<tr>
<td></td>
<td>Tourette’s syndrome (or chronic, serious tics)</td>
</tr>
<tr>
<td></td>
<td>Moderate-to-severe sensory deficits</td>
</tr>
<tr>
<td></td>
<td>Severe neurological disorders</td>
</tr>
<tr>
<td></td>
<td>Severe mood disorders (i.e., bipolar, major depression)</td>
</tr>
<tr>
<td></td>
<td>Psychotic disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Health Intervention</th>
<th>Screening/Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Outcomes Associated with the Intervention</td>
<td>Accuracy of diagnosis</td>
</tr>
<tr>
<td></td>
<td>Core symptoms (including measures of inattention, hyperactivity, impulsivity)</td>
</tr>
<tr>
<td></td>
<td>Stigma of ADHD label</td>
</tr>
</tbody>
</table>

The evidence to inform this clinical recommendation was produced by the 2009 NICE\(^{(1)}\) guideline.

From the original search only one study (Tymms 2006)\(^{(8)}\) was identified that assessed the efficacy of screening in educational settings (comparison of screening of children with ADHD as an intervention compared with no intervention). The quality of the evidence was moderate, given that only one study was included. See table 20 for further information regarding the screening trials.

In this study, teachers from 2,040 participating English primary schools completed a rating scale at the end of the children’s (N = 25,482) first year at school. The intervention involved identifying children who, at the end of the first year of school, exhibited severe ADHD symptoms, based on the cut-off points for the number of criteria deemed to represent severe ADHD symptoms as suggested in DSM-IV. The names of these pupils in half of the schools in the sample were forwarded to the new class teachers. Outcome measures were collected 18 months later, half-way through school year 2 when pupils were aged 6 to 7 years. The identification of children with severe ADHD symptoms had no detectable impact on ADHD symptoms, reading or mathematics.
The NICE(1) guideline concludes a lack of evidence to suggest that universal screening or teacher advice for children with ADHD have beneficial effects on ADHD core symptoms and conduct problems. Moreover, the evidence indicates that teacher-led interventions, such as giving effective commands, have large beneficial effects on conduct problems of children with ADHD. The beneficial effects of teacher training on children with ADHD remain inconclusive (p.224).

2. How to Evaluate for ADHD

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>2) How should children and adolescents be evaluated for ADHD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children and adolescents (aged 6 to 18 years) without a diagnosis of ADHD and who do not have any of the following:</td>
</tr>
<tr>
<td></td>
<td>f Mental retardation (or low IQ, &lt; 80)</td>
</tr>
<tr>
<td></td>
<td>f Pervasive developmental disorder</td>
</tr>
<tr>
<td></td>
<td>f Tourette’s syndrome (or chronic, serious tics)</td>
</tr>
<tr>
<td></td>
<td>f Moderate-to-severe sensory deficits</td>
</tr>
<tr>
<td></td>
<td>f Severe neurological disorders</td>
</tr>
<tr>
<td></td>
<td>f Severe mood disorders (i.e., bipolar, major depression)</td>
</tr>
<tr>
<td></td>
<td>f Psychotic disorders</td>
</tr>
<tr>
<td>Primary Health Intervention</td>
<td>Evaluation tools to diagnose ADHD</td>
</tr>
<tr>
<td>Critical Outcomes Associated with the Intervention</td>
<td>f Accuracy of diagnosis</td>
</tr>
<tr>
<td></td>
<td>f Inconvenience of tests</td>
</tr>
<tr>
<td></td>
<td>f Anxiety associated with tests</td>
</tr>
<tr>
<td></td>
<td>f False positives</td>
</tr>
<tr>
<td></td>
<td>f False negatives</td>
</tr>
<tr>
<td></td>
<td>f Stigma of ADHD label</td>
</tr>
</tbody>
</table>

The KP(3) guideline recommends the use of the DSM-5 diagnostic criteria as a part of the evaluation and diagnosis of ADHD in children and adolescents (Consensus-based). The guideline also notes that the DSM-5 diagnostic criteria are the “gold standard” for the diagnosis of ADHD (P. 19).
The publicly available Vanderbilt ADHD Rating Scales are also recommended as part of the evaluation and diagnosis of ADHD in children and adolescents. The following behavioral rating scales are optional, in addition to the initial evaluation (Consensus-Based) (p. 6):

- Conners' Rating Scales: the revised Conners' Parent Rating Scale (CPRS-R), the revised Conners' Teacher Rating Scale (CTRS-R), and the Conners'/Wells Self-Report of Symptoms rating scale (CASS)
- Achenbach Scales: CBCL, TRF, YSR
- ADHD Rating Scale - IV (ADHD RS-IV) (DSM-5-based)
- Swan, Nolan, and Pelham Questionnaire (SNAP) (DSM-5-based)

Achenbach and Vanderbilt behavioral rating scales can be utilized to assess some comorbid disorders.

Based on the systematic review provided in the guideline, as well as provider practice patterns, the GDT believes the current evidence stands.

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The recommendation is limited to the behavioral rating scales. Evaluation to determine a diagnosis of ADHD, while following the DSM-5 criteria, includes other components that were not addressed in this evidence-based guideline (i.e., physical, school, and behavioral history (including history of substance abuse); parent and student interviews; and any additional material needed for an appropriate diagnosis).
## 3. Baseline Assessments Prior to Starting Medication

| Clinical Question | 3a. How should children and adolescents with ADHD be assessed prior to starting medication to treat ADHD?  
|PRIMARY HEALTH INTERVENTION| 3b. How should children and adolescents with ADHD be assessed for cardiac risk prior to starting medication to treat ADHD?  
| | 3c. Should children and adolescents with ADHD be assessed with psychodiagnostic tests?  
| | 3d. In the absence of atopy, should children and adolescents with ADHD be referred to Allergy?  
| Population | Children and adolescents (aged 6 to 18 years) diagnosed with ADHD and not yet on medication for ADHD  
| PRIMARY HEALTH INTERVENTION | Basic physical exam assessment conducted prior to starting medication  
| | Family history of cardiovascular disease, history and physical exam for evidence of structural cardiac disease, electrocardiography, Cardiology referral  
| | Research assessment questionnaires  
| | Allergy referral, consultation and/or treatment  
| CRITICAL OUTCOMES ASSOCIATED WITH THE INTERVENTION | Important changes in weight, height, heart rate, and blood pressure  
| | Morbidity, mortality (e.g., cardiac disease, sudden death, psychosis)  
| | Reductions in core symptoms  
| | Improvements in psychosocial and educational function  
| | Core symptoms (including measures of inattention, hyperactivity, hyperactivity, impulsivity)  
| | Quality of life (clinical global impression of overall severity indices as a proxy of QoL)  
| | Educational performance (e.g., volume of work, efficiency, completion, and accuracy  
| | Psychosocial function (relationships with parents, siblings, teachers, peers)  

---

The content provided is a table that outlines the procedures and questions related to baseline assessments prior to starting medication for children and adolescents with ADHD. The table categorizes these assessments under Clinical Question, Population, Primary Health Intervention, and Critical Outcomes Associated with the Intervention. Each section is detailed with specific guidelines and considerations to ensure comprehensive care for patients with ADHD.
3a. Baseline Medical Assessments
The SIGN(2) guideline suggests “baseline physical assessment should be undertaken prior to initiation of pharmacological therapy, including, as a minimum, measurement of pulse, blood pressure, weight and height with the appropriate use of centile charts in all measured parameters.” (P.14). The guideline developers consider this a good practice point.

While NICE(1) did not provide specific evidence to support the recommendation, the guideline notes that baseline physical assessments can help rule out undiagnosed disorders with symptoms that in rare instances may mimic or cause some aspects of ADHD, such as hearing impairment, epilepsy, thyroid disorder and iron deficiency anemia. There may also be other coexisting physical, neurological and developmental disorders that should be identified (including dyspraxia, chronic tic disorders or Tourette’s syndrome, and sleep disorders) which will then shape later management (p.25). The guideline also suggests that if ADHD is diagnosed and drug therapy is considered, monitoring of height and weight, blood pressure, and pulse rate should be continued.

3b. Cardiac Risk Assessment
As NICE(1) points to risks associated with stimulants (e.g., cardiac disease, psychosis and sudden death), the guideline recommends that before starting drug treatment, children and young people with ADHD should have a full pre-treatment assessment, which should include: (not limited to) family history of cardiac disease and examination of the cardiovascular system (p.371).

The SIGN(2) guideline reports that concerns have been raised (through non-analytic studies, for example case reports and series) about a small number of sudden deaths attributed to cardiovascular events in children taking psychostimulants including methylphenidate-based and dexamphetamine-based medications in the US. Some of these cases were found to have pre-existing cardiac risk factors at autopsy, others were co-prescribed other treatments. The reported number of cases was extremely low compared with the overall number of prescriptions dispensed (FDA 2006). Psychostimulant medication results in small mean increases in pulse and blood pressure. Nonetheless, the potential harm resulting from these small increases is currently being investigated. *P.16

As such, SIGN(2) recommends that psychostimulants should not be first-line medication for children with ADHD/HKD where there are known (or where there is a family history of) cardiac abnormalities (D Grade) (P.17).† Electrocardiography should be considered on an individual case basis [depending upon physical examination findings, and medical or family history of significant cardiac abnormalities].

* Level 3 evidence: Non-analytic studies, e.g., case reports and case series.
† D Grade: Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
3c. Psychodiagnostic Tests

While noting the extensive research literature examining individual and groups of psychological assessment measures or devices (e.g., Matching Familiar Figures Test, Continuous Performance Test, Actometers), the SIGN\(^{(2)}\) guideline developers found that, in general, these measures do not distinguish children and young people with ADHD/HKD from psychiatric controls or normal peers (C Grade) \(\text{(p. 9)}\).

Observation of behavior in the clinic, while important, may be deceptive and clinicians should avoid basing diagnostic conclusions on evidence of behavior in the clinic. Standardized observational schedules for use in the home, school and laboratory setting are available; however, some practitioners find these time consuming and difficult to use. In addition, children tend to respond well in novel situations, for example, a visit to the clinic or the clinician’s visit to the home or school setting, and the results therefore may not provide an accurate picture of the child’s behavior (C grade) \(\text{(p. 9)}\).

3d. Allergy Evaluation

As neither external guideline nor the KP\(^{(3)}\) guideline investigated allergy evaluations in children and adolescents with ADHD, a systematic review identified one RCT by Pelsser\(^{(9)}\) et al (2011) that evaluated the correlation between ADHD and total IgE levels in 100 children with ADHD. The authors found that prespecified IgE immunological analyses in responders (32 of 41) and non-responders (nine of 41) in the diet group showed no association between clinical response and increased IgE blood levels. Total IgE was increased in six of 30 responders (data missing for two children) and two of nine non-responders \(\text{(p = 1.0, Fisher’s exact test)}\). Food specific IgE levels were increased in one of 31 responders (data missing for one child) and one of nine non-responders \(\text{(p = 0.41, Fisher’s exact test)}\). These results suggest that as total IgE levels were increased only in a few children, equally in responders and non-responders, the underlying mechanism of food sensitivity in ADHD (which could be related to genetic factors) is non-allergic, although the authors could not rule out the involvement of a cell-mediated allergic response.

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\* C Grade: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++.
4. First-Line Treatment Options

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>4) What are first-line pharmacological treatment options for children and adolescents diagnosed with ADHD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children and adolescents aged 6 to 18 years diagnosed with ADHD</td>
</tr>
<tr>
<td>Primary Health Intervention</td>
<td>First-line medications</td>
</tr>
<tr>
<td>Critical Outcomes Associated with the Intervention</td>
<td>Reductions in core symptoms</td>
</tr>
</tbody>
</table>

The KP(3) guideline found good evidence that methylphenidate and fair evidence that dexamethasphidate, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil are efficacious in reducing core symptoms of ADHD and, in some cases, other measures of educational and psychosocial function. The evidence on methylphenidate includes a well-designed meta-analysis on several available trials. The evidence on dexamethasphidate, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil includes a more limited number of trials.

Although there is fair evidence that adverse events do occur in children with all of these drugs, with the exception of modafinil, the benefits were determined to outweigh the risk of harm for routine use. The FDA concluded that modafinil (Provigil) causes serious side effects and denied approval for its use in pediatric patients. In February 2007, the FDA directed the manufacturers of all drug products approved for the treatment of ADHD to include in the product labeling information on possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medications, and to advise patients of precautions that can be taken (Evidence-Based: B) (p. 7).

See evidence tables on p. 115-304 of the KP(3) guideline, which contain further information regarding study/patient characteristics, results, and quality assessments.

* The GDT concludes that the intervention improves important health outcomes, based on 1) good evidence that benefits outweigh harms and costs; or 2) fair evidence that benefits substantially outweigh harms and costs.
The NICE\(^{(1)}\) guideline reports the following:

The full evidence profiles and associated forest plots can be found in Appendices 19, 18.1, 18.2, 18.3, and 18.4, respectively.

Methylphenidate in school-age children (p. 254); see Table 25 for study information and evidence summary table for trials of methylphenidate.

In school-age children, there is evidence that methylphenidate when compared with placebo or control produced a medium to large effect in reducing children’s ADHD symptoms and conduct problems. There is some indication that there is improvement in outcomes when increasing the dose.

The MTA study (MTA Co-operative Group 1999a,\(^{(10)}\) 2004a,\(^{(11)}\) 2004b,\(^{(12)}\) Jensen et al (2007)\(^{(13)}\)) began as a large (n = 579) randomized trial where children were assigned to one of the following groups: medication management, intensive behavioral treatment, combination treatment, or community care (which included medication for approximately two-thirds of the sample) (p.258).

\(\text{f}\) Medication management began with a 28-day, double blind, daily-switch titration of methylphenidate using five randomly ordered repeats each of placebo or different doses of methylphenidate (5 mg, 10 mg, 15 mg or 20 mg). Experienced (blinded) clinicians agreed the child’s initial dose after reviewing parent/teacher responses to each of the four doses. For those not responding adequately to methylphenidate during titration, alternative medications were titrated openly until a satisfactory one was found.

\(\text{f}\) Of the 289 subjects assigned to medication management (n = 144) and combined treatment (n = 145), 256 successfully completed titration. Of these, 198 (68.5%) were assigned to methylphenidate. The remaining titration completers were either openly titrated to dextroamphetamine (n = 26) or to no medication (n = 32) because of robust placebo response. The children were followed up and results of the MTA study were reported at 14, 24 and 36 months.

\(\text{f}\) At 14 months (MTA Co-operative Group, 1999a) the outcome strongly favored careful medication (whether or not in combination with behavior therapy); at that point the randomization ended, families were free to choose treatment or not, and the intensive interventions (medication monitoring and behavioral work) were discontinued.

\(\text{f}\) By the 3-year mark, the outcome was similar for all four groups.

\(\text{f}\) Adverse events at the 24- and 36-month points after randomization included influences on growth in height and weight – an effect of 0.75 inches at the 2-year mark, with no further loss at the 3-year point and (in conference reports) catch-up growth by the 8-year point, suggesting no growth suppression in that time scale.
Special circumstances – ADHD comorbid with developmental reading disorder (p. 254)

Only one study, Kupietz 1988,\(^{(14)}\) compared methylphenidate with placebo in an ADHD population comorbid with developmental reading disorder. Methylphenidate in low, medium, and high doses is effective in reducing children's ADHD core symptoms. The results suggest that methylphenidate, when compared with placebo, may reduce the risk of discontinuation.

**Adverse Events**

Methylphenidate (high dose) is more likely than placebo to cause the following side effects: insomnia, anorexia, increased irritability, moodiness, thirst, itching, diarrhea, palpitations, stuttering, negativism, reddened eyes, incoherent speech and decrease in bodyweight (Wolraich et al, 2007); see page 235. The long-term studies of methylphenidate indicate an increased risk of side effects, increase in systolic blood pressure and heart rate problems. Given the lack of background rates, the association between the use of methylphenidate and sudden death is not clear.

For individual outcomes, the quality of the evidence for methylphenidate was generally moderate to high.

**Dexamphetamine (p. 256)**

For individual outcomes, the quality of the evidence was moderate reflecting the paucity of the data. For children, NICE\(^{(1)}\) found no trials that met the quality criteria and therefore had no evidence on its efficacy.

**Atomoxetine in school-age children (p. 258)**

For individual outcomes, the quality of the evidence was generally moderate to high. See Table 27 for study information and evidence summary table for trials of atomoxetine.

There is evidence that atomoxetine has a small to medium effect in reducing ADHD core symptoms in children with ADHD, as rated by both parents and teachers. In one outcome measure (ADHD core symptoms as rated by teachers) the effect was large when children were given a high dose of atomoxetine. Regarding conduct problems, there was a small effect in the reduction of these as reported by parents and no effect when reported by teachers, although this data was only from one study (Michelson,\(^{(15)}\) et al, 2004). There is some evidence of global clinical improvement (RR = 1.46) in children taking a high dose of atomoxetine when compared with placebo groups. The evidence suggests there is a slight improvement in reducing children's conduct problems when the dose of atomoxetine is reduced.
**Adverse Events**

Some of the commonly reported side effects include nausea, cough, decreased appetite, dyspepsia, vomiting, asthenia, dizziness, pruritus, somnolence, fatigue, rash, infection, nervousness and emotional lability. There is also an increased risk of decreased appetite, dyspepsia and vomiting when dosage is augmented. The evidence suggests there is an increase of risk of discontinuation of atomoxetine when compared with placebo but this risk is not present when children are given high doses of atomoxetine.

The NICE\(^{(1)}\) safety review found seven cases of sudden death (three children and four adults) of which one had lymphocytic myocarditis and two had toxic levels of olanzapine or a possible seizure preceding death; none of these patients had prior history of cardiovascular problems or cardiovascular structural abnormalities. The review reported that none of the cases appears solely or directly attributable to atomoxetine at therapeutic doses. However, the extent of the role of atomoxetine in these deaths is difficult to establish. Further studies were being conducted by the FDA (2008b)\(^{(16)}\) at the time the NICE guideline was being prepared (January, 2008). \(p.\ 274\)

Very rarely, liver toxicity, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported. Seizures are another potential risk for atomoxetine (Eli Lilly and Company Ltd, 2008).\(^{(17)}\) Moreover, suicide-related behavior (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double-blind clinical trials, suicide-related behaviors occurred at a frequency of 0.44% in atomoxetine-treated patients (6 out of 1,357 patients treated, one case of attempted suicide and five of suicidal ideation). The age range of children experiencing these events was 7 to 12 years. There were no events in the placebo group (n = 851). It should be noted that the number of adolescent patients included in the clinical trials was low (Eli Lilly and Company Ltd, 2008). \(p.\ 258\)

**Atomoxetine versus methylphenidate** \(p.\ 274\)

One study (Wang, et al\(^{(18)}\) 2007) indicated that there is little to no difference in efficacy between methylphenidate and atomoxetine in reducing ADHD core symptoms or general clinical improvement. Another study (Newcorn,\(^{(19)}\) et al 2008) showed that osmotically released methylphenidate was more effective than atomoxetine in children’s clinical improvement. In terms of leaving the study early due to adverse events, the evidence from the two studies suggests that there is an increased risk in adverse events in children taking atomoxetine when compared with methylphenidate.

The effect sizes of the studies comparing methylphenidate with placebo ranged from SMD = -1.40 (95% CI = -1.80 to -1.01) to -0.29 (95% CI = -0.88 to 0.33). The effect sizes for atomoxetine when compared with placebo were lower, ranging from SMD = -0.44 (95% CI = -0.62 to -0.26) to -0.37 (95% CI = -0.54 to -0.19). \(p.\ 275\)
Atomoxetine is effective in reducing ADHD core symptoms and clinical improvement in school-age children with ADHD. There is no effect of atomoxetine on children’s conduct problems as rated by teachers. There is evidence suggesting that atomoxetine may increase side effects when compared with placebo and when compared with methylphenidate (p. 275).

**Special circumstances – ADHD comorbid with tic disorder (p. 275)**

Only one study (Allen et al 2005(20)) compared the effect of atomoxetine with placebo in a population of children with ADHD comorbid with tic disorder. The results indicate that there is a medium effect (SMD = -0.56) in the reduction of ADHD core symptoms as rated by parents. The Allen study also suggests that there is increased nausea, decreased appetite and risk of discontinuation in children taking atomoxetine.

In conclusion, NICE(1) reports that methylphenidate and atomoxetine are the only drugs where clear RCT evidence exists for clinical effectiveness in reducing ADHD symptoms in school-age children and young people (p.254). When compared with placebo, the size of clinical effect is largest for methylphenidate. Two studies were found that involved head-to-head comparisons between the two drugs and the result from one study by Wang et al (2007)(18) indicated that there are no significant differences in terms of its effectiveness in children with ADHD. However, in Wang, the administered dose for methylphenidate was relatively ‘small’ (0.2 to 0.6 mg/kg/day) compared with a ‘larger’ atomoxetine dose administered in the second study (0.8 to 1.8 mg/kg/day). The second study by Newcorn et al (2008)(19) showed that methylphenidate was more effective in children’s clinical improvement. Methylphenidate and atomoxetine have a similar adverse event profile with respect to effects on appetite, growth, pulse, and blood pressure requiring similar monitoring. Rarer harm events associated with atomoxetine include increased risk of suicidal behavior and hepatic damage. There is no evidence from high-quality RCTs for the efficacy of dexamphetamine in children, although there are crossover trials that show efficacy. There is some limited evidence that the off-label use of modafinil, clonidine and bupropion reduces symptoms of ADHD in children (and also does for adults) while these drugs all produce more adverse effects than placebo.

Given the lack of evidence on a clearly superior first-line stimulant medication, the KP(3) guideline recommends that when choosing a treatment, decisions should be based on clinician and parent preferences, side effects, pharmacokinetics (rapidity of onset, duration of action), cost, and formulary availability. *Evidence-based: I”.* (p. 8).

Currently, the GDT considers this topic to be a settled evidence base. As such, the GDT makes no recommendation about which of these first-line stimulant medications is most effective for the treatment of ADHD in children or adolescents (p. 9).

Due to the variance in medications offered for ADHD in the US and the UK, the GDT agreed to adopt the recommendation from the 2009 KP guideline.

* I: Insufficient evidence
5. Non-Pharmacologic Treatment Options

<table>
<thead>
<tr>
<th>Clinical Question</th>
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<tbody>
<tr>
<td>5a. Are additional educational services effective treatment options for children and adolescents diagnosed with ADHD?</td>
</tr>
<tr>
<td>5b. Are behavioral therapy/cognitive behavioral therapy (CBT), family therapy, and other skills training effective treatment options for children and adolescents diagnosed with ADHD for whom drug treatment is contraindicated?</td>
</tr>
<tr>
<td>5c. Should children and adolescents who are responding adequately to medication management be offered a clinic-based, non-drug intervention to treat core symptoms?</td>
</tr>
<tr>
<td>5d. Are dietary modifications effective for children and adolescents diagnosed with ADHD?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population</th>
<th>Children and adolescents aged 6 to 18 years diagnosed with ADHD</th>
</tr>
</thead>
</table>

| Primary Health Intervention | Supplemental educational services  
|                             | Behavioral therapy, parent and skills training  
|                             | Clinic-based, non-drug interventions (e.g., behavioral therapy/behavioral cognitive therapy, social skills training, parent training and family therapy)  
|                             | Dietary supplements and/or elimination diets |

<table>
<thead>
<tr>
<th>Critical Outcomes Associated with the Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>f Reductions in core symptoms</td>
</tr>
<tr>
<td>f Improvements in psychosocial and educational function</td>
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</tbody>
</table>

Due to the variance in educational services and therapy skills and training for ADHD offered in the US and the UK, the GDT agreed to adopt the following recommendations from the 2009 KP guideline (and not adopt/adapt from NICE\(^1\) or SIGN\(^2\)).

**Educational Services**

The 2009 KP\(^3\) guideline recommends that any educational services offered and paid for outside of KP, through the school system, are optional for all children or adolescents with ADHD. *(Consensus-Based) (p. 93)*. The GDT considers the evidence base for educational services to be stable since 2009.
Behavioral Therapy/Cognitive Behavioral Therapy (CBT), Family Therapy, And Other Skills Training

The 2009 KP(3) guideline recommends that if drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy, the following clinic-based, non-drug interventions are options for children or adolescents diagnosed with ADHD:

- Behavioral Therapy/Cognitive Behavioral Training,
- Family Therapy,
- Parent Training,
- Social Skills Training.

Consensus-Based (p. 8)

Clinical-based, non-drug intervention for children/adolescents responding to medication:

For children and adolescents who are responding adequately to medication management, the 2009 KP(3) guideline suggests that adding a clinic-based, non-drug intervention to drug treatment is not routinely recommended for treating the core symptoms of ADHD (inattention, impulsivity, or hyperactivity). Consensus-Based (p. 9)

Dietary Modifications

FDA Recommendation - FDA Panel on Linking Food Dyes and Hyperactive Kids (March 2011)

The FDA’s Food Advisory Committee has voted 11 to 3 that there is not enough evidence to conclude that artificial dyes used to color foods contribute to hyperactivity in children. However, the panel (which included outside experts in nutrition, environmental health, toxicology, food science, immunology, and psychology) did not rule out that food coloring might have a negative behavioral effect on kids. The committee agreed that more studies were needed, and it was split over whether thousands of food products that contain dyes should have to carry labels warning there may be some risk of consuming the chemical coloring. For details, please see the following links:

- Artificial dyes and hyperactivity in children
- Evaluation of Studies on Artificial Food Colors and Behavior Disorders in Children

The NICE(1) guideline presented epidemiological research that indicates a link between food additives and preservatives in the diet and levels of hyperactivity (McCann(21) et al., 2007). The notion is that one or more substances triggering adverse reactions can affect susceptible children.
The McCann study was a double-blinded placebo-controlled crossover trial of food additives in 3-year-old and 8- and 9-year-old children. Results of this study suggest an association between food additives (artificial colors, sodium benzoate, or both) and increased levels of ADHD symptoms in the child populations studied. “These studies indicate short-term toxic effects of food additives on the level of ADHD symptoms in children, whether they have ADHD or not and might contribute towards significant impairment in some cases. There is no indication that food additives cause long-term effects on child development.” (pgs. 227-8).

NICE(1) reported that other trials have addressed multiple idiosyncratic reactions to additives, focusing either on tartrazine, or on mixed additives, or on a range of potentially harmful substances that can vary from child to child (p. 227).

- Conners(22) et al (1976) found a significant difference between a ‘Feingold diet’ (excluding artificial additives and natural salicylates) and a ‘placebo’ diet; but the generalizability was limited by unexplained order effects and by doubts over whether there was adequate disguise of the treatment allocation (thereby affecting the overall quality of the study).
- Harley(23) et al (1978) reported a similar comparison, with enhanced measures to preserve the disguise, and found no consistent effects.
- Williams(24) et al (1978) used a crossover design to compare the elimination of additives, methylphenidate, and placebo in children (N = 26) who were known to be responders to stimulant medication. They found that the diet was superior to ‘placebo’ but inferior to medication.

NICE(1) also identified four RCTs that examined the possibility that individual children with ADHD may be adversely affected by food that would not influence the behavior of most children with ADHD (p. 228).

- Two studies (Egger et al. (1985)(27) and Carter et al. (1993)(28)) used open trials to identify foods that affected individual children, and then introduce those identified substances in double-blind crossover design. The incriminated foods varied substantially between children, and included natural foods (for example, cows’ milk, wheat flour, citrus fruit, eggs) as well as artificial colorings and preservatives.
- Both studies indicated that the results of the open trial could be replicated in a double-blind design: some children were helped by individually designed elimination diets, at least in the short term.
- One of the studies suggested that children’s responsiveness to incriminated foods was predicted by parents’ informal observations (Carter et al., 1993).
- Two studies (Kaplan et al. (1989); Schmidt et al. (1997)(30)) randomly allocated young people to a diet excluding the most common-provoking substances or a ‘normal’ diet. Both are limited by small numbers and one (Schmidt et al) by an inpatient sample; but both imply the superiority of the elimination diet.
However, dietary modifications for the treatment of ADHD have not been satisfactorily addressed by clinical trials. As such, NICE\(^{(1)}\) reports that such diets are potentially difficult for some families to manage, and might lead to unbalanced diets and nutritional problems. “Good clinical practice suggests that such diets should be embarked on with professional advice and subject to clinical assessment of the child’s needs” \(\textbf{(p. 228)}\).

NICE\(^{(1)}\) concluded that the quality of evidence for dietary interventions is generally poor, reflecting the paucity of the data. The evidence that elimination diets when compared with placebo may reduce ADHD symptoms is inconclusive \(\textbf{(p. 229)}\).

SIGN\(^{(2)}\) reports that some food colorants and preservatives can have adverse effects on children in the general population as well as those with ADHD. The guideline suggests that avoiding foods and drinks that contain certain artificial colors and/or preservatives may benefit some children with ADHD.

\(\text{f}\) In two studies of children aged three years and eight/nine years, mixed artificial colorants (sunset yellow, tartrazine, carmoisine and ponceau 4R) or the preservative sodium benzoate, or both, exacerbated hyperactive behaviors as rated by parents. \(\text{f}\) The authors found that the nature of the responses were individual and appeared to have a pharmacological rather than an allergic mechanism (Bateman\(^{(31)}\) et al (2004), McCann\(^{(21)}\) et al (2007)). \(\textbf{(p. 23)}\)

\(\text{f}\) A meta-analysis by Benton et al (2007)\(^{(32)}\) of additive-free diets followed by food challenges in children with hyperactive disorders showed that pathological responses to foods were multiple and idiosyncratic, although the most common responses were to the artificial colorant tartrazine and the preservative sodium benzoate. \(\textbf{(p. 23)}\)

The guideline recommends that parents be advised to take reasonable steps to limit the number and variety of these in their children’s diets, excluding any item that seems to provoke an extreme physical or behavioral reaction \(\textbf{(p. 23)}\).
6. Second-Line Pharmacologic Treatment Options

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>6) What are the second-line pharmacologic treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children and adolescents aged 6 to 18 years diagnosed with ADHD</td>
</tr>
<tr>
<td>Primary Health Intervention</td>
<td>Second-line treatment medications</td>
</tr>
<tr>
<td>Critical Outcomes Associated with the Intervention</td>
<td>Reductions in core symptoms</td>
</tr>
<tr>
<td></td>
<td>Improvements in psychosocial and educational function</td>
</tr>
</tbody>
</table>

The KP\(^{(3)}\) guideline recommends that if two or more first-line stimulant formulations are contraindicated, not tolerated, or ineffective; the second-line non-stimulant treatment atomoxetine or guanfacine is an option. (Evidence-based: C)\(^{(p. 8)}\).

There is fair evidence that atomoxetine is efficacious in reducing core symptoms of ADHD. Long-term placebo-controlled or open-label follow-up studies demonstrating efficacy or overall safety have not been conducted on atomoxetine in children or adolescents with ADHD. Therefore, atomoxetine is included as the second-line treatment option. In addition, warnings on hepatotoxicity and suicidality from atomoxetine exist. In 2005, the FDA directed Eli Lilly (Lilly) to include a boxed warning on the label for Strattera on an increased risk of suicidal thinking in children and adolescents. (See BOXED WARNING in Appendix G.) In February 2007, the FDA directed the manufacturers of all drug products approved for the treatment of ADHD to include in the product labeling information on possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medications, and to advise patients of precautions that can be taken. Patients and caregivers should be instructed to recognize the signs and symptoms of liver dysfunction, as well as of cardiovascular and psychiatric adverse events. Liver function tests can also be considered for children or adolescents prescribed atomoxetine.

* The GDT makes no recommendation for or against the intervention. Evidence is sufficient to determine the benefits, harms and costs of an intervention, and there is at least far evidence that the intervention improves important health outcomes. But the GDT concludes that the balance of the benefits, harms and costs is too close to justify a general recommendation.
The GDT agrees that this evidence base is stable. However, as the above noted recommendation was based on evidence from a literature search through June 2009, the KP guideline project management team performed a literature refresh from November 2009 to November 2011 for the following eight second-line medications:

**Atomoxetine**

§ In an 8-week, double blind, placebo-controlled RCT of atomoxetine in 101 children (5 and 6 years of age) with ADHD, Kratochvil(33) et al (2011) found significant mean decreases in parent (P = 0.009) and teacher (P = 0.02) ADHD-IV Rating Scale scores 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 = 0.1). 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 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. Despite benefits, the children in the atomoxetine group remained, on average, significantly impaired at the end of the study.

§ Wietecha(34) et al (2009) compared two atomoxetine titration dosing schedules and two atomoxetine maintenance doses for treating adolescent ADHD. Adolescents (N = 267) were randomized to a slow or fast titration schedule. Patients who responded continued on a 40-week maintenance treatment, randomized to 0.8 or 1.4 mg/kg/day. During the acute period, significant benefit was demonstrated with both titration schedules on the ADHD Rating Scale total score. Although patients in both groups maintained benefit relative to week 0, statistically significant loss of benefit was found for patients maintained on 0.8 mg/kg/day but not on 1.4 mg/kg/day. A similar pattern was observed on the Clinical Global Impressions-ADHD-Severity scores and Life Participation Scale for ADHD-Child Version scores. Mean grades for most subjects improved for patients in both maintenance treatment groups although most improvements were not statistically significant. The results indicate that in adolescents with ADHD, treatment benefit at 8 weeks was better maintained long-term with 1.4 mg/kg/day than with 0.8 mg/kg/day.

§ Takahashi(35) et al (2009) randomized a total of 245 Japanese children and adolescents with ADHD, aged 6 to 17 years, to receive placebo or one of three atomoxetine doses (0.5, 1.2, and 1.8 mg/kg per day) over 8 weeks. In all, 234 patients completed the study. Atomoxetine at 1.8 mg/kg per day was significantly superior to placebo in reducing ADHD symptoms (p = 0.01; one-sided). Decreased appetite and vomiting were significantly greater in the atomoxetine treatment groups; however, no clinically significant differences were observed. Two patients discontinued due to affect lability and headache.
Through a randomized, placebo-controlled, double blind trial, Marteny(36) et al (2010) compared the efficacy and tolerability of once-daily atomoxetine (≤ 1.8 mg/kg day) with those of placebo in children and adolescents (aged 6 to 16 years) with attention-deficit/hyperactivity disorder [ADHD (DSM-IV)]. Compared with patients in the placebo group (n = 33), patients treated with atomoxetine (n = 72) with a mean final dose of 1.4 mg/kg showed significantly greater improvement in ADHDRS-IV-Parent: Inv total score (least-squares mean: atomoxetine = -15.8; placebo = -11.4; p = 0.013). The most common treatment related adverse events in the atomoxetine group included anorexia [atomoxetine, n = 13 (18.1%); placebo, n = 2 (6.1%)], somnolence, n = 11 versus n = 3 (15.3% vs. 9.1%, respectively), abdominal pain n = 9 versus n = 1 (12.5% vs. 3.0%, respectively) and nausea, n = 8 versus n = 1 (11.1% vs. 3.0%, respectively). Seven patients in the atomoxetine group and two in the placebo group experienced clinically important weight loss during the study (≥ 7% from baseline; mean change, kg: atomoxetine, -0.6; placebo, 0.1; p = 0.032). The results suggest that atomoxetine is efficacious in improving ADHD symptoms in children and adolescents.

Guanfacine

Connor(37) et al (2010) found that in 217 children (aged 6 to 12 years) randomized to receive guanfacine XR (1 to 4 mg/day) or placebo for nine weeks, reduction in ADHD-RS-IV total score from baseline to endpoint was observed in guanfacine treated group (23.8 vs. 11.5, p < 0.0001, effect size = 0.92). The most common treatment emergent adverse events were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%), and fatigue (11%), mild-moderate in severity. Most subjects receiving guanfacine demonstrated modest changes in blood pressure, pulse rate, and ECG readings but those changes were not deemed clinically significant.

An RCT by Rostain(38) et al (2009) evaluated the safety and efficacy of extended release guanfacine (GXR) in the treatment of ADHD in 345 children aged 6 to 17 years. Participants were required to have electrocardiogram (ECG) and blood pressure results in the normal range. Patients were randomized to one of three treatment groups (2, 3, or 4 mg/d) or placebo. There were statistically significant differences among the treatment groups (p < 0.0001), with a mean reduction in ADHD-RS-IV scores across the three GXR treatment groups of -16.7, compared with -8.9 for placebo. Significant improvement in Clinical Global Impression Improvement (CGII) of scores was noted in 26% of the placebo participants and 50% to 56% of the GXR-treated participants. Adverse events were mild, with the most commonly reported adverse effects being somnolence, fatigue, sedation, and upper abdominal pain, mostly of mild or moderate intensity.
Sallee\(^{(39)}\) et al (2009) randomized 6 to 17 year olds to guanfacine XR (1 to 4 mg/per day) or placebo. Reductions in ADHD rating scale-IV were observed from baseline to endpoint at all doses of GXR, with relative reduction in rating scale score ranging from 0.43 to 0.62. Mean heart rate and systolic and diastolic blood pressure decreased as the dose of GXR increased and then returned toward baseline during the dose-maintenance and dose tapering phases of the trial. The most frequent treatment emergent adverse events were somnolence, sedation, headache, fatigue, dizziness, upper abdominal pain, nausea, irritability. Somnolence, sedation and fatigue emerged within the first two weeks of dosing and generally resolved by study end.

### Clonidine

Kollins\(^{(40)}\) et al (2011) randomized 1978 children to receive CLON-XR plus stimulant (102) or placebo (96). At week 5, greater improvement from baseline on ADHD Rating Scale IV (95% CI: -7.83 to 1.13), p = 0.09), ADHD RS-IV hyperactivity and inattention subscale scores (p = 0.014 and p = 0.017, respectively). Adverse events and changes in vital signs in the CLON-XR group were mild.

Jain\(^{(41)}\) et al (2011) randomized 236 children and adolescents to receive placebo (78), CLON-XR 0.2 mg/day (78) or CLON-XR 0.4 mg/day (80). Improvement from baseline in ADHD Rating Scale-IV was significantly better in both CLON-XR groups versus placebo at week 5. Improvement in inattention and hyperactivity subscales, Conners Parent Rating Scale, Revised, occurred in both treatment groups versus placebo. The most common adverse effect was mild to moderate somnolence and changes on electrocardiogram were minor and reflected the known pharmacology of clonidine.

### Adverse Effects

(KP Drug Monograph on Clonidine, p. 9-10)

The most common adverse events reported were: somnolence, fatigue, upper respiratory tract infection, irritability, sore throat, insomnia, nightmares, emotional disorder, constipation, nasal congestion, increased body temperature, dry mouth and ear pain.

Hypersensitivity to clonidine hydrochloride has been identified as a contraindication.

Several warnings / precautions exist:

- Hypotension, bradycardia, sedation, somnolence, abrupt discontinuation, allergic reactions
- Use with caution in patients with severe coronary insufficiency, conduct disturbances, recent myocardial infarction, cerebrovascular disease or chronic renal failure.
- Do not take with other clonidine hydrochloride products.
- Although no studies evaluating the effect of abrupt discontinuation in children being treated with clonidine XR have been conducted, dose tapering is recommended. Abrupt discontinuation: Physicians should gradually reduce the dose in decrements of no more than 0.1 mg every 3 to 7 days to avoid withdrawal effects.
Bupropion

One small trial by Daviss et al. (2005) evaluated drug pharmacokinetics in 11 boys and 8 girls aged 11 to 17 years old prescribed bupropion SR monotherapy for ADHD (n = 16) and/or depressive disorders (n = 16). Bupropion (and its metabolites) exhibited linear pharmacokinetics. Areas under the concentration curves for the hydroxybupropion, threohydrobupropion, and erythrohydrobupropion were 20, 12, and 2.7 times higher, respectively, than for bupropion. Relative to adults, the mean half-lives of bupropion (12.1 hours) and threohydrobupropion (26.3 hours) were significantly shorter, and areas under the concentration curve ratios of metabolites to bupropion were 19% to 80% higher. The five other studies identified were not relevant to this clinical question.

Imipramine

Out of six recent studies found, two were most relevant. One study (Clark et al, 2008) investigated the effects of imipramine hydrochloride on the EEG of children. The other (Jadad et al, 1999) was a narrative review that sought to determine (a) the long-term and short-term effectiveness and safety of pharmacological and non-pharmacological interventions for ADHD in children and adults and (b) whether combined interventions are more effective than individual interventions.

- Out of 77 RCTs, 23 studies compared drugs and showed few, if any, differences among methylphenidate (MPH), dextroamphetamine (DEX), and pemoline; studies comparing stimulants with tricyclic antidepressants were inconclusive.

- Six studies compared drugs with non-drug interventions and showed consistently that stimulants, particularly MPH, may be more effective than non-pharmacological interventions.

- Twenty studies compared combination therapies with a stimulant or a non-drug intervention alone; no additional beneficial effects for combination therapies were shown.

- Nine studies compared tricyclic antidepressants with placebo and showed that desipramine may be more effective than placebo; no consistent effect was shown for imipramine.

- Fourteen studies (13 in school children and 1 in adults) evaluated long-term therapy (≥12 weeks) and showed a trend to general improvement regardless of treatment, but the length of follow-up was inadequate. MPH may reduce behavioral disturbance in children with ADHD while it is taken.

- Academic performance does not appear to be improved with stimulants.

- Thirty-two reports (29 studies) evaluated adverse effects of drug therapy; many of the side effects associated with stimulant use appear to be relatively mild and of short duration and to respond to dosing or timing adjustments. Data are inadequate on the long-term effects and severity of adverse effects of most interventions.
Venlafaxine

Of the three studies found, two were most relevant. An RCT by Zarinara (2010) investigated the efficacy and tolerability of venlafaxine compared to methylphenidate in 38 children and adolescents with ADHD. The results suggested no significant differences between the treatment groups. The other study (Findling et al, 2007) was an open-label trial that explored the changes in symptom severity, tolerability, and the pharmacodynamics of venlafaxine treatment in 38 youths with ADHD. The results indicate that venlafaxine appeared to offer some benefit and appears to be relatively safe for the short-term treatment of ADHD in this open-label trial.

Nortriptyline

One RCT by Prince et al (2000) examined the efficacy and tolerability of nortriptyline in the treatment of pediatric ADHD in 35 children and teens. At the conclusion of the discontinuation phase, the 12 subjects randomized to nortriptyline had significantly lower scores on the DSM-IV ADHD symptom checklist than those 11 subjects randomized to placebo (31 versus 21; t = 2.2; p < 0.04). No significant adverse events were observed, and children were noted to have weight gain during the trial.

Desipramine

Four recent studies were found, two were most relevant. One study by Bloch et al (2009) evaluated desipramine in children with ADHD and tics and found that alpha-2 agonists and atomoxetine significantly improved comorbid tic symptoms. Although there was evidence that supratherapeutic doses of dextroamphetamine worsened tics, there was no evidence that methylphenidate worsened tic severity in the short term. A study (Spencer, 2002) evaluated the tolerability and efficacy of desipramine hydrochloride in the treatment of children and adolescents with chronic tic disorders and comorbid ADHD. Treatment with desipramine (mean total daily dose, 3.4 mg/kg per day) was well tolerated without meaningful adverse effects. Desipramine significantly reduced core symptoms of ADHD (ADHD Rating Scale; 42% decrease from baseline relative to placebo, P < 0.001), with equal response in inattentive symptoms and hyperactive/impulsive symptoms (P < 0.001 for both). The ADHD response rate was robust (71% vs. 0%; desipramine vs. placebo, P < 0.001). Likewise, desipramine significantly reduced tic symptoms (Yale Global Tic Severity Scale; 30% decrease from baseline relative to placebo, P < 0.001), with equal response in motor and phonic tic symptoms (P < 0.01 for both). The tic response rate was substantial (58% vs. 5%; desipramine vs. placebo, P < 0.001). There were small but statistically significant differences between desipramine and placebo in heart rate and blood pressure.
NICE
The NICE(1) guideline notes that further treatment may include the use of medication unlicensed for the treatment of ADHD (such as bupropion, clonidine, modafinil, and imipramine) or combination treatments (inc. psychological treatments for the parent or caregiver and the child or young person). The use of medication unlicensed for ADHD should only be considered in the context of tertiary services (p. 372, section 12.5.6.4). (See the GRADE Evidence Profiles for more information.)

In 2000, the Royal College of Pediatrics and Child Health(50) issued a policy statement on the use of unlicensed medicines, or the use of licensed medicines for unlicensed applications, in children and young people. This stated clearly that such use is necessary in pediatric practice and that doctors are legally allowed to prescribe unlicensed medicines where there are no suitable alternatives and where the use is justified by a responsible body of professional opinion.

Clonidine
See Table 28 on page 276 for study information and evidence summary. For individual outcomes, the quality of the evidence was moderate reflecting the paucity of the data. Two trials were identified that included a comparison of clonidine with placebo. One trial (Hazell(51) et al, 2003) was done with a sample of school-age children with ADHD (common coexisting conditions included oppositional defiant disorder and/or conduct disorder). The second study (Kurlan(52) et al, 2002) involved adults with ADHD and comorbid Tourette’s syndrome, chronic motor tic disorder or chronic vocal tic disorder. The Kurlan study also included a comparison of clonidine with methylphenidate. The evidence suggests that clonidine reduces children’s ADHD core symptoms and conduct problems as well as producing general clinical improvement. When outcomes were measured by teachers, the effect sizes were medium; when measured by parents, they were small to no effect.

Bupropion
See Table 29 on page 281 for study information and evidence from the important outcomes and overall quality of evidence. Of the 49 trials, five included a comparison of bupropion with placebo. Two of these studies recruited school-age children with ADHD (a common coexisting condition was conduct disorder). Three trials involved adults with ADHD (common coexisting conditions included major depression, anxiety disorders and antisocial personality disorder).

For individual outcomes, the quality of the evidence was generally moderate to high. In school-age children, there is no statistically significant evidence that bupropion reduces ADHD core symptoms or behavior in children with ADHD. One study reports an increase of rash in children taking bupropion when compared with placebo. When compared with placebo, bupropion may increase the risk of discontinuation. Thus, there is no evidence that bupropion is effective in reducing ADHD core symptoms or conduct problems in children with ADHD. There is limited evidence that bupropion may increase the risk of rash.
Modafinil
For individual outcomes, the quality of the evidence was generally moderate to high. See Table 30 for study information and evidence summary table for trials of modafinil.

Of the 49 studies included, only five involved a comparison of modafinil with placebo. All trials were of school-age children with ADHD (common coexisting conditions included oppositional defiant disorder, conduct disorder, learning disorder, phobias and separation anxiety).

Overall, the evidence shows that modafinil, when compared with placebo, has a medium effect in reducing ADHD symptoms and conduct problems as well as producing general clinical improvement.

Adverse Events (p. 285)
Reported side effects include “dry mouth, appetite changes, gastro-intestinal disturbances (including nausea, diarrhea, constipation and dyspepsia), abdominal pain; tachycardia, vasodilatation, chest pain, palpitation; headache (uncommonly migraine), anxiety, sleep disturbances, dizziness, depression, confusion, abnormal thinking, parasthesis, agitation, asthenia; visual disturbances; less commonly mouth ulcers, glossitis, pharyngitis, dysphagia, taste disturbance, hypertension, hypotension, bradycardia, arrhythmia, peripheral edema, hypercholesteroolemia, rhinitis, dyspnea, dyskinesia, amnesia, emotional lability, abnormal dreams, tremor, decreased libido, weight changes, hyperglycemia, urinary frequency, menstrual disturbances, eosinophilia, leucopenia, myasthenia, muscle cramps, dry eye, sinusitis, epistaxis, myalgia, arthralgia, acne, sweating, rash, and pruritus” (British Medical Association & the Royal Pharmaceutical Society of Great Britain, 2007;53 Cephalon UK Limited, 200854). For modafinil, statistically significant adverse events and/or with an RR greater than 5% are displayed in Table 30. For a full list of adverse events see the forest plot in Appendix 18.

Antidepressants (p. 289)
TCAs have significant side effects and high toxicity in overdose. Concerns regarding potential cardiotoxicity of desipramine have led to its withdrawal in the UK. There is limited evidence that SSRIs and SNRIs may increase the risk of suicidal ideation and/or behavior.

There is no evidence that TCAs, SSRIs or SNRIs are of value in the treatment of the symptoms of ADHD.
SIGN
The SIGN\(^{(2)}\) guideline developers conducted a review of guanfacine use in children with ADHD and notes that while early industry trials suggest efficacy in treatment of symptoms, there is insufficient evidence on which to base a recommendation. The major adverse effects were sedation, fatigue, dry mouth, headache and sleep disturbance. There is also a possibility that as the dose of guanfacine increases, blood pressure and pulse may be lowered.

While an unlicensed medication to treat ADHD in the UK, clonidine can be considered in children unresponsive to or unable to tolerate treatment with psychostimulants or atomoxetine. It may be used on its own or in combination with methylphenidate on an individual case basis (p. 20). SIGN - Guanfacine - insufficient evidence; Clonidine - Grade C.

Two RCTs (Hazell\(^{(51)}\) et al, 2003; Palumbo\(^{(55)}\) et al, 2008) found that clonidine reduced ADHD/HKD symptoms, and that this reduction was greater when clonidine was taken in combination with methylphenidate than when taken on its own. Clonidine was either given three times a day up to a maximum dose of 0.6 mg daily depending on response and adverse effects, or twice a day at total dose of 0.10 to 0.20 mg/day (Hazell, 2003). In one study individuals who had received clonidine had a greater reduction in systolic blood pressure measured standing than controls, and had transient sedation and dizziness (Hazell, 2003).

As a good practice point, the guideline suggests that clinicians should monitor pulse and blood pressure, and check for signs of over-sedation in patients prescribed clonidine and discontinuation should be carried out gradually to avoid the risk of rebound hypertension (p. 20).
7. Monitoring of Medications

| Clinical Question | 7a. How often should children and adolescents with ADHD be seen and evaluated by a prescribing clinician?
|                  | 7b. Should patients and caregivers be advised of potential harms associated with stimulants? |
| Population       | Children and adolescents aged 6 to 18 years diagnosed with ADHD |
| Primary Health Intervention | Evaluation during medication treatment Monitoring for adverse events during medication treatment |
| Critical Outcomes Associated with the Intervention | f Reductions in core symptoms f Improvements in psychosocial and educational function |

**Monitoring Frequency**
To stay consistent with HEDIS measures for ADHD, the GDT agreed to adopt the current KP(3) guideline recommendation of one in-person office visit with a practitioner with prescriptive authority for children age 6 to 12 years during the 30-day initiation phase of drug treatment for ADHD.

**Instruction on Adverse Events**
The KP(3) guideline suggests that assessment for adverse effects, adherence to treatment, and response to treatment is recommended during the follow-up visit. Patients and/or caregivers should monitor for changes in core symptoms of ADHD (hyperactivity, impulsivity, and inattention), educational function, psychosocial function, and potential side effects such as headaches, abdominal pain, and changes in height, weight, blood pressure, pulse, or eating and sleeping patterns. *(Consensus-Based)* *(p. 10)*

NICE*(1)* reported that the 2006 FDA review of ADHD medicines revealed a slight increased risk (about 1 per 1,000) for drug-related psychiatric adverse events, such as hearing voices, becoming suspicious for no reason, or becoming manic, even in patients who did not have previous psychiatric problems. In February 2007, the FDA directed the manufacturers of all drug products approved for the treatment of ADHD to develop ‘*Patient Medication Guides*’ to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines, and to advise them of precautions that can be taken *(p. 233)*.
8. Drug Holidays

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>8) Are drug holidays recommended for children and adolescents diagnosed with ADHD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children and adolescents aged 6 to 18 years diagnosed with ADHD</td>
</tr>
<tr>
<td>Primary Health Intervention</td>
<td>Continuation or cessation of medication</td>
</tr>
</tbody>
</table>
| Critical Outcomes Associated with the Intervention | $f$ Reductions in core symptoms  
$f$ Improvements in psychosocial and educational function |

The NICE\(^{(1)}\) guideline notes that drug holidays are not routinely recommended; however, consideration should be given to the parent or caregiver and child or young person with ADHD working with their healthcare professional to find the best pattern of use, which may include periods without drug treatment (\textit{P. 314}).

In a NICE-sponsored focus group study of children and young people’s experiences with psychostimulant medication, NICE\(^{(1)}\) notes that a few children queried in this group reported taking drug holidays at weekends and school holidays. In addition, some felt they had the option to stop taking tablets if they wanted to (\textit{p. 487}). Follow-up data to determine the presence of complications or adverse events following intermittent drug holidays was not provided.
9. Drug Continuations

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>9) How long should children and adolescents with ADHD continue medication treatment?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children and adolescents aged 6 to 18 years diagnosed with ADHD</td>
</tr>
<tr>
<td>Primary Health Intervention</td>
<td>Duration of medication management</td>
</tr>
<tr>
<td>Critical Outcomes Associated with the Intervention</td>
<td>$\checkmark$ Reductions in core symptoms $\checkmark$ Improvements in psychosocial and educational function</td>
</tr>
</tbody>
</table>

The NICE\(^{(1)}\) guideline developers note the limited empirical evidence that is available to guide clinicians on the optimum duration of treatment and when to consider drug discontinuation. However, NICE\(^{(1)}\) suggests that for people taking methylphenidate, atomoxetine or dexamphetamine, height should be measured every six months in children and young people and weight should be measured three and six months after drug treatment has started and every six months thereafter in children and young people (pgs. 311 and 377).

SIGN\(^{(2)}\) does not address the question of optimal duration of treatment but addresses drug discontinuation, for which the pediatrician and/or psychiatrist is responsible. “The pediatrician and/or psychiatrist will advise the general practitioner (GP) when medication should be discontinued in children receiving long term drug therapy. The specialist will provide necessary supervision and support during the drug discontinuation phase.” (p. 39). This recommendation is based on expert opinion, and thus the quality of evidence is very low.
### 10. ADHD and Comorbidities

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>10) Should children and adolescents with ADHD be referred to a specialist when presenting with comorbidities?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Children and adolescents aged 6 to 18 years diagnosed with ADHD</td>
</tr>
<tr>
<td>Primary Health Intervention</td>
<td>Specialty referral</td>
</tr>
</tbody>
</table>
| Critical Outcomes Associated with the Intervention | $f$ Reductions in core symptoms  
$f$ Improvements in psychosocial and educational function |

Although insufficient evidence is available to recommend for or against the interventions as an optimal treatment strategy, the GDT chose to make a consensus recommendation regarding referral to or consultation with a specialist, such as a behavioral pediatrician, ADHD champion, or child psychiatrist. Such referral is an option for children with common comorbid conditions such as anxiety, depression, oppositional defiant disorder, conduct disorder, or severe tics, and for additional treatment options that may include clinic-based behavioral interventions and other drug therapy regimens to treat the comorbid symptoms (p. 107). This recommendation is based on the 2009 KP(3) guideline.

Specialty referral for children and adolescents with ADHD was not addressed in the NICE(1) guideline.

However, if based on preliminary assessment, it is suspected that a child or young person has ADHD associated with significant impairment, SIGN(2) recommends that referral for specialist assessment by a child an adolescent mental health clinician or pediatrician with a specialist interest in this field is recommended (p. 7).
### Appendix C: ADHD Guideline Recommendation Matrix

The GDT translated evidence appraisal language into terms consistent with GRADE terminology to achieve consistency with evidence quality assessments contained in the guidelines reviewed in the AGREE process and to meet the standards of the KP National Guidelines Program.

To determine the overall strength of the recommendations, the GDT assigned equal weight to the four GRADE domains (see below). For example, when less uncertainty (in balance of harms to risks, differences in values and preferences, and net benefits and costs) and higher quality evidence were identified in three or four of the four domains, the GDT assigned a strong recommendation. Otherwise, the GDT considered the recommendation as weak.

#### Preliminary Comparison of External Guideline Recommendations

<table>
<thead>
<tr>
<th>Topics / Interventions</th>
<th>KP</th>
<th>SIGN</th>
<th>NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whom to screen?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Referral</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>How to screen?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychological Testing</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Neurological Testing</td>
<td></td>
<td>X</td>
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</tr>
<tr>
<td>Treatment</td>
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<tr>
<td>Topics / Interventions</td>
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<tr>
<td>Combined Drug Therapy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Length of Treatment with Medications in Patients</td>
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<td>X</td>
</tr>
<tr>
<td>Monitoring of psychopharmacological interventions</td>
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<tr>
<td>Initiation, titration and dosing</td>
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</tr>
<tr>
<td>Side effects</td>
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<tr>
<td>Sexual dysfunction</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Tachycardia, arrhythmia</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Psychotic symptoms</td>
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<td></td>
<td>X</td>
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<tr>
<td>Seizures</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Topics / Interventions</th>
<th>KP</th>
<th>SIGN</th>
<th>NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment school-age child</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Second-line treatment – Preschool-age child</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Moderate or mild impairment</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Severe impairment</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>First-line treatment adolescents - Moderate impairment</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Second-line treatment – School-age child</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mild or moderate impairment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe impairment</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>School based interventions</td>
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<tr>
<td>Drug Treatment</td>
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<td>Prescriber knowledge</td>
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<tr>
<td>Pre-drug assessment</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Choice of Drug/Specific Drug Recommendations</td>
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<tr>
<td>Stimulants</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Topics / Interventions</td>
<td>KP</td>
<td>SIGN</td>
<td>NICE</td>
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<td>------------------------</td>
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<tr>
<td>Tics</td>
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</tr>
<tr>
<td>Anxiety</td>
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<tr>
<td>Height/weight</td>
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<tr>
<td>Diversion</td>
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</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
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<tr>
<td>Other treatment interventions</td>
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<td></td>
<td>X</td>
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<tr>
<td>Non-Drug Interventions</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Combined Drug and Non-Drug Therapy</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nutrition</td>
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<td>X</td>
</tr>
<tr>
<td>Information, consent, the law and support for people with ADHD and their caregivers</td>
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<td></td>
<td>X</td>
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<tr>
<td>Training of healthcare professionals</td>
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<td></td>
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<tr>
<td>Co-morbid psychiatric conditions</td>
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<td>Evaluation</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Treatment - Conduct disorders</td>
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</table>

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<table>
<thead>
<tr>
<th>Topics / Interventions</th>
<th>KP</th>
<th>SIGN</th>
<th>NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended release preparations</td>
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</tr>
<tr>
<td>Methylphenidate</td>
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<tr>
<td>Atomoxetine</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Dexamphetamine</td>
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</tr>
<tr>
<td>Clonidine</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</table>

<table>
<thead>
<tr>
<th>Topics / Interventions</th>
<th>KP</th>
<th>SIGN</th>
<th>NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment - Comorbid oppositional defiant disorder</td>
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<td></td>
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<tr>
<td>Treatment - Comorbid generalized anxiety</td>
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<tr>
<td>Anti-depressants</td>
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<tr>
<td>Desipramine</td>
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<td>X</td>
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<tr>
<td>Unlicensed medications</td>
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<td></td>
<td>X</td>
</tr>
</tbody>
</table>
### Detailed Comparison of Recommendations

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>KP 2011 Draft Recommendation</th>
<th>External GL Sources/Additional Literature Searches</th>
<th>GL Rationale Statement</th>
<th>GRADE Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who (children/adolescent) should be screened for ADHD?</td>
<td>1. Universal screening for ADHD is not recommended.</td>
<td>NICE 2008</td>
<td>There is no evidence to indicate that universal screening or teacher advice for children with ADHD have beneficial effects on ADHD core symptoms and conduct problems (p. 226).</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RCT (screening v. no screening, p. 2010) - the identification of children with severe ADHD symptoms had no detectable impact on ADHD symptoms, reading or mathematics. Thus, the evidence suggests that there is little to no effect in introducing a screening program on children's ADHD symptoms or academic</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>&quot;There is no evidence to indicate that universal screening or teacher advice for children with ADHD have beneficial effects on ADHD core symptoms and conduct problems. The evidence indicates that teacher-led interventions, such as giving effective commands, have large beneficial effects on conduct problems of children with ADHD. The beneficial effects of teacher training on children with ADHD remain inconclusive.&quot; P.224</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of Evidence: Moderate-low (NICE appraised the Quality of Evidence as moderate (given that one study was included in the assessment (p. 211) while SIGN's screening recommendation was based on expert opinion (p. 7)).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Values and Preferences: The GDT believes that caregivers and patients would generally weigh the benefits of diagnosis and treatment in children and adolescents suspected of having ADHD greater than the risks associated with screening and universal screening. Variation in patient acceptance of screening in children or adolescents with signs, symptoms, or impairments suggestive of ADHD is likely to be low.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cost (Resource Utilization): Low</td>
<td></td>
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</tbody>
</table>

* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>KP 2011 Draft Recommendation</th>
<th>External GL Sources/Additional Literature Searches</th>
<th>GL Rationale Statement</th>
</tr>
</thead>
</table>
| 2. Screening for ADHD is recommended in children with signs, symptoms, or impairment suggestive of ADHD. | SIGN 2009 | Good practice point, based on expert opinion. | “The initial presentation will usually be to general practitioners, or to other primary care, education and social work professionals. Important information can be obtained at this stage which will suggest the need for specialist investigation. Those involved in carrying out the initial assessment must be aware of the prevalence and core features of ADHD/HKD as well as some of the difficulties encountered in making the diagnosis, including issues of comorbidity and the impact of situation/environment on presentation. Key areas to explore at this stage include:  
  - The nature of the problem: are the presenting problems of the type represented by the diagnostic criteria for ADHD/HKD?  
  - The severity of the problem (dysfunction in a number of domains, including family, education and social). If, on the basis of preliminary assessment, it is suspected that a child or young person has ADHD/HKD associated with significant impairment, referral for specialist assessment by a child and adolescent mental health clinician or pediatrician with a specialist interest in this field is recommended.” P. 7 |

* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
### Clinical Question

How should children and adolescents be screened for ADHD?

### KP 2011 Draft Recommendation

3. As part of the evaluation and diagnosis of ADHD in children and adolescents, clinicians should use structured, validated rating scales † and refer to and follow the DSM-5 diagnostic criteria.

### External GL Sources/Additional Literature Searches

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<thead>
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</thead>
<tbody>
<tr>
<td>KP 2009</td>
<td>Use of the DSM-5 diagnostic criteria as a part of the evaluation and diagnosis of ADHD in children and adolescents is recommended (p. 7)</td>
<td>Consensus-based</td>
<td></td>
<td></td>
<td></td>
<td>Strong</td>
</tr>
</tbody>
</table>

#### Rationale

**Balance Between Desirable And Undesirable Effects:** There are substantial benefits in utilizing DSM IV criteria and other validated tools for evaluation and diagnosis of ADHD in children and adolescents and low risk of harm. School and developmental history and parent/child interviews, for example, may also be considered.

**Quality of Evidence:** High (the recommended diagnostic criteria and tools are well-validated, as noted in the previous KP guideline (p. 12).

**Values and Preferences:** The GDT believes that variation in caregiver or patient acceptance of the type of diagnostic criteria used for ADHD evaluation is likely to be low.

**Cost (Resource Utilization):** Low

* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)

† The publicly available Vanderbilt ADHD Rating Scales are recommended as part of the evaluation and diagnosis of ADHD in children and adolescents. The following behavioral rating scales are options to be used in addition to the initial evaluation: Conners’ Rating Scales (the revised Conners’ Parent Rating Scale (CPRS-R), the revised Conners’ Teacher Rating Scale (CTRS-R), and the Conners’/Wells Self-Report of Symptoms rating scale (CASS)), Achenbach Scales: CBCL, TRF, YSR, ADHD Rating Scale – IV (ADHD RS-IV) (DSM-5-based), Swan, Nolan, and Pelham Questionnaire (SNAP) (DSM-5-based), and Achenbach and Vanderbilt behavioral rating scales can be utilized to assess some comorbid disorders.
<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>KP 2011 Draft Recommendation</th>
<th>External GL Sources/Additional Literature Searches</th>
<th>GL Rationale Statement</th>
<th>GRADE Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>How should children and adolescents be screened for ADHD?</td>
<td>Baseline physical assessment (including measurement of pulse, blood pressure, weight and height with the appropriate use of percentile charts) is recommended prior to initiating pharmacological therapy.</td>
<td>GLs Used to Formulate Recommendation</td>
<td>SIGN 2009</td>
<td>Pharmacology therapy - in addition to baseline assessment, clinicians should provide information about potential benefits and adverse effects of medications and the continuing benefit from and need for medication should be assessed at least once per year (p. 20)</td>
</tr>
</tbody>
</table>
**Clinical Question**: How should children and adolescent be screened for ADHD?

**KP 2011 Draft Recommendation**: Cardiac risk evaluation is recommended prior to prescribing psychostimulants for children or adolescents with ADHD with known cardiac abnormalities.

**External GL Sources/Additional Literature Searches**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>KP 2009 NICE 2008 SIGN 2009 - Disagreement with SIGN GL (which was consensus/case study based). New recommendation for 2011.</td>
<td>KP-FDA Warnings for ADHD Pharmacologic Treatments - “Adderall generally should not be used in patients with structural cardiac abnormalities” (p. 323) SIGN-Psychostimulants should not be first-line medication for children with ADHD/HKD where there are known (or where there is a family history of) cardiac abnormalities (p. 23) NICE- Before starting drug treatment, children and young people with ADHD should have a full pre-treatment assessment, which should include: (not limited to) family history of cardiac disease and examination of the cardiovascular system (p. 371)</td>
<td>Case series/reports and expert opinion</td>
<td>AHRQ sponsored study - In 2011, the results from a retrospective cohort study (Cooper et al) of automated health plan data for over 1.2 million participants aged 2-24 found no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events (adjusted hazard ratio, 0.75; 95% CI [CI], 0.31 to 1.85). Within the total participant population, cohort members had 81 serious cardiovascular events (3.1 per 100,000 person-years). Although the point estimates of the relative risks for ADHD drugs do not indicate increased risk, the upper limit of the 95% CI suggests that a doubling in the risk could not be ruled out. However, the absolute magnitude of any increased risk would be low. The low number of events limited the statistical power of the study, particularly for individual end points and individual drugs, as well as for subgroups that might be particularly vulnerable to the effects of ADHD drugs.</td>
<td>SIGN - “Concerns have been raised about a small number of sudden deaths attributed to cardiovascular events in children taking psychostimulants including methylphenidate based and dexamphetamine based medications in the US. Some of these cases were found to have pre-existing cardiovascular risk factors at autopsy, others were co-prescribed other treatments. The reported number of cases was extremely low compared with the overall number of prescriptions dispensed. Psychostimulant medication results in small mean increases in pulse and blood pressure. The potential harm as a result of this is currently being investigated.” P. 16 NICE - see source document column</td>
<td>Balance Between Desirable And Undesirable Effects: Stimulant medication therapy for ADHD has been traditionally contraindicated in patients with known cardiac abnormalities. The CDT agrees that the risks of cardiac risk evaluation prior to initiation of psychostimulant therapy are generally low, and that children or adolescents with cardiac abnormalities have or will likely be referred to Cardiology for evaluation for reasons other than ADHD. As cardiac risk has been discussed in the literature, the NICE guideline also considers the balance between desirable and undesirable effects by reporting that before drug treatment initiation, children and young people with ADHD should have a full pre-treatment assessment, which should include (but is not limited to) family history of cardiac disease and examination of the cardiovascular system as well as an electrocardiogram (ECG) if there is past medical or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination (p. 304). Continued next page</td>
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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
Continued from previous page, GRADE Components column.

In 2011, the results from an AHRQ-funded retrospective cohort study by Cooper et al. (insert reference as footnote) of automated health plan data for over 1.2 million participants aged 2-24 found no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events (adjusted hazard ratio, 0.75; 95% CI: 0.31 to 1.85). Within the total participant population, cohort members had 81 serious cardiovascular events (3.1 per 100,000 person-years). Although the point estimates of the relative risks for ADHD drugs do not indicate increased risk, the upper limit of the 95% CI suggests that a doubling in the risk could not be ruled out. However, the absolute magnitude of any increased risk would be low. The low number of events limited the statistical power of the study, particularly for individual end points and individual drugs, as well as for subgroups that might be particularly vulnerable to the effects of ADHD drugs. In considering this recent AHRQ study and its implications, despite the low risk in absolute terms for an individual patient, the GDT felt that a potential doubling of the relative risk of stimulants in this population outweighs the risk of cardiac risk assessment.

**Quality of Evidence:** Very Low Quality of Evidence from the guidelines reviewed (recommendations from KP (p. 75) and NICE (p. 304) are based on case reports and expert opinion, while SIGN's recommendation (p.16,19) is based on Grade D evidence (extrapolate evidence)). With the addition of the AHRQ review, the quality of the evidence improves to low-moderate.

**Values and Preferences:** The GDT believes that patients and caregivers would generally weight the benefits of evaluating a child or adolescent's risk for cardiac events greater than the potential risk of adverse events or potential costs associated with the evaluation. Thus variation here is likely to be low.

**Cost (Resource Utilization):** Low-moderate, based upon insurance coverage of the patient/family, family financial resources and specifics of patient and family past history. The systems cost for Kaiser Permanente may be variable, based on variation in additional workup ordered in the cardiac risk assessment.
### Clinical Question

**How should children and adolescents be screened for ADHD?**

Laboratory assessments are not routinely recommended as part of ADHD screening in the absence of other indications.

### External GL Sources/Additional Literature Searches

|--------------------------------------|-----------------------------------------------------|-------------------------------------|-----------------------------------|------------------------|------------------------
| SIGN 2009                            | Laboratory assessments should not be used routinely (pg 15). | C Grade (A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++). Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal. | |

**GL Evidence Grade, Basis of Evidence**

- **C Grade**: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++. Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.

**Updated Literature Searches (2011)**

- Laboratory assessment measures (e.g., Matching Familiar Figures Test, Continuous Performance Test, Actometers). In general these measures do not distinguish children and young people with ADHD/HKD from psychiatric controls or normal peers.

**GL Rationale Statement**

- "There is extensive research literature examining individual and groups of laboratory assessment measures (e.g., Matching Familiar Figures Test, Continuous Performance Test, Actometers). In general these measures do not distinguish children and young people with ADHD/HKD from psychiatric controls or normal peers. Observation of behavior in the clinic, whilst important, may be deceptive and clinicians should avoid basing diagnostic conclusions on evidence of behavior in the clinic. Standardized observational schedules for use in the home, school and laboratory setting are available; however, some practitioners find these time consuming and difficult to use. In addition, children tend to respond well in novel situations, e.g., a visit to the clinic or the clinician’s visit to the home or school setting, and the results therefore may not provide an accurate picture of the child’s behaviour." P. 9

### GRADE Components *

- **Balance Between Desirable And Undesirable Effects**: In the absence of other indications, research laboratory assessments do not confer significant benefits as part of the evaluation and diagnosis of ADHD. The SIGN guideline reports that while there is extensive research literature examining individual and groups of laboratory assessment measures, in general these measures do not distinguish children and young people with ADHD/HKD from psychiatric controls or normal peers.

- **Quality of Evidence**: Low (SIGN’s recommendation is based on C grade evidence (p. 9)).

- **Values and Preferences**: The GDT believes that variation in caregiver or patient acceptance of the use of laboratory assessments for the evaluation of ADHD is likely to be low.

- **Cost (Resource Utilization)**: Low

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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)

† C grade evidence equates with a body of evidence including studies rated as 2+; well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
|-------------------|-------------------------------|-----------------------------------------------|---------------------------------|---------------------------------|------------------------|
| **What are first-line treatment options for treatment of ADHD in children and adolescents?** | **Stimulant medications methylphenidate, amphetamine mixed salts, and dextroamphetamine are recommended as first-line treatment for children and adolescents diagnosed with ADHD (with or without comorbid conditions).** | **GLs Used to Formulate Recommendation**
KP 2009 | **Source Document/GL Recommendation & Page Reference**
Based on the available evidence, the GDT recommends the use of stimulants (e.g., methylphenidate preparations, amphetamine preparations) as a first-line treatment option for children and adolescents diagnosed with ADHD (p. 9). | **Evidence-Based B, based on systematic review or meta-analysis** | "There is good evidence that methylphenidate and fair evidence that dexmethylphenidate, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil are efficacious in reducing core symptoms of ADHD and, in some cases, other measures of educational and psychosocial function. The evidence on methylphenidate includes a well-designed meta-analysis on several available trials. The evidence on dextroamphetamine, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil includes a more limited number of trials. Although there is fair evidence that adverse events do occur in children with all of these drugs, with the exception of modafinil, the benefits were determined to outweigh the risk of harm for routine use.** |

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<table>
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<tr>
<th><strong>GRADE Components</strong></th>
<th><strong>Recommendation Strength</strong></th>
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| **Strong** | **Balance Between Desirable and Undesirable Effects:**

There is good evidence that methylphenidate and fair evidence that dexmethylphenidate, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil are efficacious in reducing core symptoms of ADHD and, in some cases, other measures of educational and psychosocial function. Although there is fair evidence that adverse events do occur in children and adolescents with all of these drugs, the exception of modafinil, the benefits were determined to outweigh the risk of harm for routine use. **(Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)**

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National ADHD Clinical Practice Guideline
The KP guideline notes good evidence that methylphenidate and fair evidence that dexmethylphenidate, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil are efficacious in reducing core symptoms of ADHD and, in some cases, other measures of educational and psychosocial function. The evidence on methylphenidate includes a systematic review and meta-analysis on several available trials (King et al, 2006(56) and Schachter et al., 2001(57)). The evidence on dexmethylphenidate, dextroamphetamine, mixed-amphetamine salts, lisdexamphetamine dimesylate, and modafinil includes a more limited number of trials. Although there is fair evidence that adverse events do occur in children with all of these drugs, with the exception of modafinil, the benefits were determined to outweigh the risk of harm for routine use (p. 7)

**Quality of Evidence:** Moderate (the KP guideline lists the evidence as grade B (p. 28)).

**Values and Preferences:** The GDT believes that there may be variation in patient acceptance of first-line medication because of tolerability issues with stimulants.

**Cost (Resource Utilization):** Low (for generic stimulants)
<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>KP 2011 Draft Recommendation</th>
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<tbody>
<tr>
<td><strong>What are first-line treatment options for treatment of ADHD in children and adolescents?</strong></td>
<td>When selecting a first-line therapy, treatment decisions should be based on clinician, patient and/or caregiver preferences, side effects, pharmacokinetics (rapidity of onset, duration of action), cost, and formulary availability. Advise parents or other caregivers and children/adolescents diagnosed with ADHD of potential harms associated with stimulants and encourage collaborative treatment decision-making with a physician.</td>
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<td><strong>The (2009) GDT makes no recommendation about which of these first-line stimulant medications is most effective for the treatment of ADHD in children or adolescents (p. 9).</strong></td>
<td>KP 2009</td>
<td>Insufficient evidence to determine which medication is most effective.</td>
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**GRADE Components**

*Balance Between Desirable and Undesirable Effects:*
Given the lack of evidence on a clearly superior first-line stimulant medication, the GDT agrees that when choosing a treatment, decisions should be based on clinician and parent preferences, side effects, pharmacokinetics (rapidity of onset, duration of action), cost, and formulary availability (KP ADHD Guideline, 2009, p. 7). This shared decision-making approach will also prove beneficial when informing the patient and caregiver of potential side effects and harms associated with stimulant treatment. The substantial benefits of such a collaborative approach outweigh risk of harm.

**Quality of Evidence:** Very Low (the KP guideline labels the evidence as insufficient (p. 28)).

**Values and Preferences:** The GDT believes that variation in caregiver or patient acceptance of shared decision making approach in selecting among first-line stimulant preparations likely to be low.

**Cost (Resource Utilization):** Low

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*(Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)*

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National ADHD Clinical Practice Guideline
### Clinical Question

What are first-line treatment options for treatment of ADHD in children and adolescents?

### Clinical Question Answer

Additional educational services offered outside of KP, such as through the school system, are recommended for children or adolescents diagnosed with ADHD.

### External GL Sources/Additional Literature Searches

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<tbody>
<tr>
<td>KP 2009</td>
<td>Non drug treatment (p. 83)</td>
<td>Expert opinion</td>
<td></td>
<td>“Any educational services offered and paid for outside of KP, through the school system, are recommended for all children or adolescents with ADHD.” P. 93</td>
</tr>
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### GRADE Components

The GDT acknowledges the difficulty patients may experience accessing such services, especially if offered through the public school system (given the variability of available resources across different school systems and the difficulties of assessing the quality and consistency of such services).

**Balance Between Desirable And Undesirable Effects:**

The benefits conferred to a child or adolescent with ADHD seeking educational services offered outside KP (e.g., in a school setting) would likely outweigh serious harm. The GDT agrees that supplemental services may augment clinic-based treatment and help address educational or psychosocial issues observed in children or adolescents diagnosed with ADHD.

**Quality of Evidence:** Very Low (the KP recommendation is based on expert opinion (p. 81)).

**Values and Preferences:** The GDT believes that variation in patient and caregiver acceptance of seeking additional educational services outside KP is likely to be low.

**Cost (Resource Utilization):** Varies, depending on type of educational facility (e.g., public versus private facility). The KP guideline notes these services as offered and paid for outside of KP (p. 93).

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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
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<tr>
<td>What are first-line treatment options for treatment of ADHD in children and adolescents?</td>
<td>11. Behavioral therapy/cognitive behavioral therapy (CBT), family therapy, parent training, and social skills training are options for children or adolescents diagnosed with ADHD, with or without comorbidities, for whom drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy.</td>
<td>11. Behavioral therapy/cognitive behavioral therapy (CBT), family therapy, parent training, and social skills training are options for children or adolescents diagnosed with ADHD, with or without comorbidities, for whom drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy.</td>
<td>KP 2009</td>
<td>Non drug treatment - p. 10</td>
<td>Expert opinion</td>
<td></td>
<td>&quot;If drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy, the following clinic-based, nondrug interventions are options for children or adolescents diagnosed with ADHD:</td>
<td>Balance Between Desirable And Undesirable Effects: The benefits conferred to a child or adolescent with ADHD seeking proven clinic-based non-drug interventions (e.g., behavioral therapy/cognitive behavioral therapy (CBT), family therapy, parent training, and social skills training) when medication treatment is contraindicated, not tolerated, or not desired would likely outweigh risk of harm. The GDT agrees that the use of those clinic-based, non drug interventions would likely benefit those children or adolescents with ADHD unable to benefit from pharmacologic therapy. Harm could be incurred by patients and families seeking interventions (e.g., from the internet) whose effectiveness has not been rigorously evaluated. The previous KP guideline found that given the limited evidence available directly comparing non-drug interventions with drug treatment, drug treatment appears to be more favorable over non-drug interventions. However, clinic-based non-drug interventions are options for children or adolescents for whom drug treatment is contraindicated, not tolerated, or a decision has been made not to initiate drug therapy. (p. 92).</td>
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*(Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)*
### Clinical Question

For children and adolescents who are responding adequately to medication management, adding a clinic-based, non-drug intervention is not routinely recommended for treating the core symptoms of ADHD (e.g., inattention, impulsivity, or hyperactivity).

### External GL Sources/Additional Literature Searches

<table>
<thead>
<tr>
<th>GLs Used to Formulate Recommendation</th>
<th>Source Document/ GL Recommendation &amp; Page Reference</th>
<th>GL Evidence Grade, Basis of Evidence</th>
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<tbody>
<tr>
<td>KP 2009</td>
<td>Combined Drug And Nondrug Treatment - p. 11</td>
<td>Expert opinion</td>
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### Updated Literature Searches (2011)

- "For children and adolescents who are responding adequately to medication management, adding a clinic-based, non-drug intervention to drug treatment is not routinely recommended for treating the core symptoms of ADHD (inattention, impulsivity, or hyperactivity). Consensus-Based" p. 9

### GL Rationale Statement

- **Balance Between Desirable and Undesirable Effects**: When children and adolescents are responding well to medication management, the GDT agrees that the addition of clinic-based non-drug interventions for treating the core symptoms of ADHD will not yield significant benefits. The KP guidelines notes that the potential harms and costs of routinely adding non-drug interventions to successful drug treatment outweigh any potential, but still unknown, benefits (p. 97).

- **Quality of Evidence**: Very low (the KP recommendation is based on expert opinion (p. 11).

- **Values and Preferences**: Given that patients and/or caregivers may be interested in exploring non-medication treatment pathways, variation in patient and caregiver acceptance of this recommendation may be low to moderate.

- **Cost (Resource Utilization)**: Low-moderate, depending on insurance benefit.

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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
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<tr>
<td>What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?</td>
<td>Second-line treatment options After assessing for and addressing medication adherence and other conditions that might interfere with response, if not otherwise contra-indicated, a second stimulant medication (in the same or different class) is recommended for patients who fail to adequately respond to or are intolerant to the initial stimulant.</td>
<td>KP 2009 Guanfacine recommendation is consistent with NICE and SIGN</td>
<td>KP 2009 - Evidence-Based: C and I (the GDT makes no recommendation for/or against intervention). SIGN - A review of guanfacine use in children with ADHD notes that early industry trials suggest efficacy in treatment of symptoms. The major adverse effects were sedation and fatigue. Dry mouth, headache and sleep disturbance were also common. As the dose of guanfacine increases, blood pressure and pulse may be lowered. There is insufficient evidence on which to base a recommendation for guanfacine.</td>
<td>Guanfacine literature refresh (Nov 2009-Nov 2011) 1. Connor 2010 [77] 217 children (aged 6 to 12 years) were randomized to receive guanfacine XR (1 to 4 mg/day) or placebo for 9 weeks. Reduction in ADHD-RS-IV total score from baseline to endpoint was observed in guanfacine treated group (23.8 vs. 11.5, p &lt; 0.0001, effect size = 0.92). Most common treatment emergent adverse events were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%), fatigue (11%), mild-moderate in severity. Most subjects receiving guanfacine demonstrated modest changes in blood pressure, pulse rate, and ECG readings those changes were not deemed clinically significant.</td>
<td>Guanfacine literature refresh (Nov 2009-Nov 2011) 1. Connor 2010 [77] 217 children (aged 6 to 12 years) were randomized to receive guanfacine XR (1 to 4 mg/day) or placebo for 9 weeks. Reduction in ADHD-RS-IV total score from baseline to endpoint was observed in guanfacine treated group (23.8 vs. 11.5, p &lt; 0.0001, effect size = 0.92). Most common treatment emergent adverse events were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%), fatigue (11%), mild-moderate in severity. Most subjects receiving guanfacine demonstrated modest changes in blood pressure, pulse rate, and ECG readings those changes were not deemed clinically significant.</td>
<td>* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)</td>
<td><strong>Balance Between Desirable And Undesirable Effects:</strong> Unless contraindicated, the benefits conferred in prescribing a second stimulant medication (replacing one stimulant medication with another) would likely outweigh the harms when patients are unresponsive to or are intolerant to first-line treatment. The GDT agrees that the benefits of stimulants for the treatment of ADHD are well-documented and the use of a second stimulant (in the same or different class) would likely benefit patients unresponsive to first-line treatment. There is no evidence to suggest a preferred order of trial of medications. The second-line medication options listed in the guideline have been evaluated and have been generally found to be safe, although as with stimulants, each is associated with specific side-effects. The GDT also notes that consultation after two medication failures is a common and reasonable clinical strategy with a low risk of undesirable effects. <strong>Quality of Evidence:</strong> Low (KP guideline labels evidence as Grade C/insufficient (p. 8, 99). <strong>Values and Preferences:</strong> The GDT believes that variation in patient and caregiver acceptance of the recommended second-line treatment options, including consultation is likely to be low-moderate.</td>
</tr>
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</table>
### Clinical Question

**What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?**

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>KP 2011 Draft Recommendation</th>
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<tr>
<td>If two or more first-line stimulant formulations are contraindicated, not tolerated, or ineffective, treatment options include Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral health pediatrician or ADHD champion. Stimulant treatment augmented with guanfacine or clonidine Guanfacine or clonidine monotherapy The non-formulary medication atomoxetine</td>
<td><strong>If two or more first-line stimulant formulations are contraindicated, not tolerated, or ineffective, treatment options include Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral health pediatrician or ADHD champion. Stimulant treatment augmented with guanfacine or clonidine Guanfacine or clonidine monotherapy The non-formulary medication atomoxetine</strong></td>
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### External GL Sources/Additional Literature Searches

|--------------------------------------|-----------------------------------------------------|------------------------------------|-----------------------------------|------------------------|
| Clonidine (unlicensed medication) can be considered in children unresponsive to or unable to tolerate treatment with psychostimulants or atomoxetine. It may be used on its own or in combination with methylphenidate on an individual case basis (p. 20). | **NICE**-p.372 (unlicensed medications) | treatments for routine use in children and adolescents diagnosed with ADHD: Bupropion, Imipramine, Clonidine, Venlafaxine, Nortriptyline (clonidine was removed from KP 2009 after review of NICE, SIGN, and Clonidine monograph from KP). The balance of the benefits and harms is too close to justify a general recommendation for routine use of desipramine in children and adolescents diagnosed with ADHD. (KP 2009) | Continued on next page. **Continued on next page.** 2. Rostain 2009 (38) This RCT evaluated the safety and efficacy of extended release guanfacine in the treatment of ADHD in 345 children aged 6 to 17 years. Participants were required to have electrocardiogram (ECG) and blood pressure results in the normal range. Patients were randomized to one of three groups (2, 3 or 4 mg/d) or placebo. There were statistically significant differences among the treatment groups (P < 0.0001), with a mean reduction in ADHD-RS-IV scores across the three GXR treatment groups of -16.7, compared with -8.9 for placebo. Significant improvement in Clinical Global Impression of Improvement scores was noted in 26% of the placebo participants and 50% to 56% of the GXR-treated | **GRADE Components**

**Cost (Resource Utilization):** Low (for substitution of one formulary stimulant for another) to moderate (for combined drug treatment, use of second-line medication options), or added costs due to additional referral. **Continued on next page.**

**Continued on next page.**
### Clinical Question
What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?

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<tbody>
<tr>
<td>KP Drug Monograph, Guanfacine, March 2010</td>
<td>Continued from previous page, GL Evidence Grade, Basis of Evidence column</td>
<td>Continued from previous page, GL Evidence Grade, Basis of Evidence column</td>
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**Contraindications/precautions** - patients with a history of hypersensitivity to guanfacine; use guanfacine with caution in patients at risk for hypotension, bradycardia, heart block or syncope; measure heart rate and blood pressure periodically during treatment; advise patients to avoid becoming dehydrated or overheated.

**Special populations** - safety and efficacy in patients < 6 years have not been established. For children and teens ≥ 6 years, efficacy beyond nine weeks and safety beyond two years of treatment have not been established.

**Continued on next page.**
What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?

Clonidine hydrochloride is excreted in breast milk. In a study of nursing women taking clonidine, hypotension was not observed in the infants. However, the long-term effect of this exposure has not been determined. It is recommended that nursing mothers exercise caution when taking clonidine XR.

Continued on next page.
Continued from previous page, GL Evidence Grade, Basis of Evidence column

The effect of renal impairment has not been studied in children taking clonidine XR. For patients with renal impairment taking the IR formulation, half-life can increase up to 41 hours. It is recommended that patients with renal impairment should be monitored for hypotension and bradycardia and the dose titration should be done cautiously. Patients with renal impairment are recommended to have their dosage adjusted based on the level of impairment and be monitored for adverse events.

The effect of hepatic impairment has not been studied in children taking clonidine XR. About 50% of the absorbed dose clonidine hydrochloride is hepatically metabolized. Dose-adjustment may be necessary for patients with significant hepatic impairment.

Continued from previous page, Updated Literature Searches (2011) column

Nortriptyline - One RCT (2000) was found that studied the efficacy and tolerability of nortriptyline (NT) in the treatment of pediatric ADHD in 35 children and teens. At the conclusion of the discontinuation phase, the 12 subjects randomized to NT had significantly lower scores on the DSM-IV ADHD symptom checklist than those 11 subjects randomized to placebo (31 versus 21; t = 2.2; p < 0.04). No significant adverse events were observed, and children were noted to have weight gain during the trial.

Desipramine - Four recent studies were found, three most relevant. One study evaluated desipramine in children with ADHD and tics, another in children with ADHD and Tourette's Syndrome. A final study was a narrative review of the effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with ADHD.
### Clinical Question

What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?

### KP 2011 Draft Recommendation

One in-person office visit with a practitioner with prescriptive authority is recommended for children and adolescents during the 30-day initiation phase of drug treatment for ADHD.

### External GL Sources/Additional Literature Searches

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<tr>
<td>KP 2009</td>
<td>KP Monitoring drug treatment - p. 11</td>
<td>KP guideline recommendation follows HEDIS, more stringent than SIGN (Expert opinion, no good evidence to guide recommendation)</td>
<td></td>
<td>“One in-person office visit with a practitioner with prescriptive authority is recommended for children age 6 to 12 years during the 30-day initiation phase of drug treatment for ADHD. Assessment for adverse effects, adherence to treatment, and response to treatment is recommended during the follow-up visit. Monitor for changes in core symptoms of ADHD (hyperactivity, impulsivity, inattention), educational function, psychosocial function, and potential side effects such as headaches, abdominal pain, and changes in height, weight, blood pressure, pulse, or eating and sleeping patterns. Consensus-Based” p. 10</td>
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<tr>
<td>SIGN 2009</td>
<td>SIGN- pgs.11, 12, 14, 39</td>
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### GRADE Components *

- **Balance Between Desirable And Undesirable Effects:** In patients on stimulant therapy, ongoing follow-up affords the clinician an opportunity to gauge adverse events, treatment adherence, and response to treatment with low risk of harm. Despite the lack of evidence on an optimal follow-up interval, the current KP guideline recommends following the current 2009 HEDIS standard to support the organization’s quality and accreditation initiatives related to the monitoring of ADHD medications (p. 110).

- **Quality of Evidence:** Very Low (KP recommendation is based on HEDIS measures while SIGN is based on expert opinion (p. 39).

- **Values and Preferences:** The GDT believes that variation in patient and caregiver acceptance of recommended monitoring intervals is likely to be low.

- **Cost (Resource Utilization):** Low to moderate

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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)

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National ADHD Clinical Practice Guideline
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<tr>
<td>What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?</td>
<td>Instruct patients and/or other caregivers about signs and symptoms of liver dysfunction, cardiovascular events, and suicidality. Liver function tests is optional for patients prescribed atomoxetine.</td>
<td>GLs Used to Formulate Recommendation</td>
<td>Source Document/ GL Recommendation &amp; Page Reference</td>
<td>RCT Cohort/case-control studies Case series/reports</td>
<td>KP - &quot;Assessment for adverse effects, adherence to treatment, and response to treatment is recommended during the follow-up visit. Monitor for changes in core symptoms of ADHD (hyperactivity, impulsivity, inattention), educational function, psychosocial function, and potential side effects such as headaches, abdominal pain, and changes in height, weight, blood pressure, pulse, or eating and sleeping patterns. Consensus-Based&quot; p. 10</td>
<td>Balance Between Desirable And Undesirable Effects: There are potentially significant benefits in advising patients and caregivers to recognize signs and symptoms of adverse events associated with stimulant treatment, with low risk of harm.</td>
<td>Strong</td>
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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
<table>
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<tr>
<th>Clinical Question</th>
<th>KP 2011 Draft Recommendation</th>
<th>External GL Sources/Additional Literature Searches</th>
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| What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment? | Clinicians should assess the continuing benefit from and need for medication at least every six months. Following an adequate treatment response, drug treatment for ADHD should be continued for as long as it remains clinically effective. | GLs Used to Formulate Recommendation: SIGN 2009, NICE 2008  
Little empirical evidence is available to guide clinicians on questions such as the optimum duration of treatment and when it is appropriate to consider drug discontinuation. (NICE 2009)  
Source Document/GL Recommendation & Page Reference: SIGN- The continuing benefit from and need for medication should be assessed at least once per year (good practice point) (p. 14)  
NICE-drug holidays, p. 314  
GL Evidence Grade, Basis of Evidence: Expert opinion  
Updated Literature Searches (2011):  
GL Rationale Statement:  
GRADE Components *  
Balance Between Desirable And Undesirable Effects: The GDT agrees that benefits incurred from conducting routine assessments on medication need and continuation would far outweigh risks. The SIGN guideline notes that the continuing benefit from and need for medication should be assessed at least once per year (p. 14).  
Quality of Evidence: Very Low (SIGN recommendation is a good practice point, based on expert opinion (p. 14).  
Values and Preferences: Variation in patient and caregiver preferences for routine medication assessments is likely to be low.  
Cost (Resource Utilization): Low  
Recommendation Strength: Weak |

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<tr>
<td>What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?</td>
<td>Drug holidays are not routinely recommended. However, clinicians should consider the viewpoints of the parent/caregiver and patient with ADHD to identify the best pattern of use, which may include periods without drug treatment.</td>
<td>NICE 2009</td>
<td>NICE-drug holidays, p. 314</td>
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<td>&quot;Drug holidays are not routinely recommended; however, consideration should be given to the parent or caregiver and child or young person with ADHD working with their healthcare professional to find the best pattern of use, which may include periods without drug treatment.&quot; P. 314. &quot;A few children reported taking drug holidays at weekends and school holidays. A few children felt they had the option to stop taking tablets if they wanted to.&quot; P. 487</td>
<td><em>Balance Between Desirable And Undesirable Effects:</em> As ADHD medication should be continued as long as effective and drug holidays have not been shown to be generally beneficial, risks associated with medication cessation or drug holiday might outweigh the benefits. The NICE guideline notes that while drug holidays are not routinely recommended consideration should be given to the parent or caregiver and child or young person with ADHD working with their healthcare professional to find the best pattern of use, which may include periods without drug treatment (p. 276). <em>Quality of Evidence:</em> Very Low (NICE recommendation is based on expert opinion (p. 314). <em>Values and Preferences:</em> While the GDT does not recommend drug holidays, the team believes that consideration should be given to identifying the best pattern of use, which may include periods without treatment. Patients and families may express a diversity of opinions regarding drug holidays; variation in patient and caregiver preferences may be significant.</td>
<td>Weak</td>
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**Clinical Question:** What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?

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<td>Referral or consultation with a specialist, including child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion is an option for children or adolescents with common comorbid conditions such as oppositional defiant disorder and conduct, anxiety, and tic disorders.</td>
<td>KP 2009 SIGN 2009 Some level of EB, supported by SIGN</td>
<td>KP: p. 22, 115 SIGN: comorbidities, p. 7, 9</td>
<td>RCT Case series/reports</td>
<td>KP - “Although insufficient evidence is available to recommend for or against the interventions as an optimal treatment strategy, the GDT chose to make a consensus recommendation that referral or consultation with a specialist, such as a behavioral pediatrician, ADHD champion, or child psychiatrist, is an option for children with common comorbid conditions such as anxiety, depression, oppositional defiant disorder, conduct disorder, or severe tics, for additional treatment options that may include clinic-based behavioral interventions and other drug therapy regimens to treat the comorbid symptoms.” P. 107 SIGN - “If, on the basis of preliminary assessment, it is suspected that a child or young person has ADHD/HKD associated with significant impairment, referral for specialist assessment by a child and adolescent mental health clinician or pediatrician with a specialist interest in this field is recommended.” P. 7</td>
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**External GL Sources/Additional Literature Searches**

**GRADE Components**

* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)

| **Balance Between Desirable And Undesirable Effects:** Benefits are expected when a child or adolescent with ADHD and a concomitant comorbidity are referred to specialty care or others expert in ADHD treatment, given the complexities of comorbidity. The current KP guideline notes that in cases where improvements in ADHD symptoms are not seen in children or adolescents with comorbid conditions after first-line and second-line treatment has been tried, a referral to a sub-specialist (e.g., child psychiatry, behavioral health, a behavioral pediatrician, or ADHD champion) for more treatment options is recommended (p. 100).  
**Quality of Evidence:** Moderate-Very Low (KP and SIGN recommendations are based on a limited number of RCTs (KP, p. 22, 115) while SIGN’s language is based on expert opinion (p. 7, 9, 27).  
**Values and Preferences:** The GDT believes that patients would generally weigh the benefits of referral or consultation to a specialist greater than the costs or risk of not seeking referral and/or treatment when a child or adolescent with ADHD presents with a comorbidity. Any variation in patient and caregiver acceptance is likely to be low.  
**Cost (Resource Utilization):** Low-moderate, based upon the insurance coverage of the patient/family.

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National ADHD Clinical Practice Guideline
## Clinical Question

What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?

## KP 2011 Draft Recommendation

Dietary supplements and elimination diets are not indicated for the treatment of ADHD.

## External GL Sources/Additional Literature Searches

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<td>NICE 2008</td>
<td>SIGN 2009</td>
<td>SIGN-food additives: There is evidence from well controlled studies that some food colorants and preservatives can have adverse behavioral effects on children both in the general population and in those diagnosed with ADHD/HKD (p. 23) NICE-p. 29, 112, 139 FDA Recommendation- FDA Panel Says No Support for Linking Food Dyes, Hyper Kids (March 2011). But the panel, which included outside experts in nutrition, environmental health, toxicology, food science, immunology, and psychology did not rule out that food coloring might have a negative behavioral effect on kids. The committee agreed that more studies need to be done, and split over whether thousands of food products that contain dyes should have to carry labels warning there may be some risk of consuming the chemical coloring.</td>
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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
### Clinical Question
What are second-line treatment options for children and adolescents with ADHD who fail to adequately respond to initial treatment?

### KF 2011 Draft Recommendation
In the absence of signs or symptoms of atopy, allergy evaluation, referral, or treatment is not indicated for ADHD.

### External GL Sources/Additional Literature Searches

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<td>SIGN 2009</td>
<td>Not a referral recommendation but an overall good practice point: Avoiding foods and drinks that contain certain artificial colors and/or preservatives may help some children with ADHD/HKD. Parents should be advised to take reasonable steps to limit the number and variety of these in their children's diets, excluding any item that seems to provoke an extreme physical or behavioral reaction (p. 23).</td>
<td>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. In two studies in non-clinical populations of children aged three years and eight/nine years, mixed artificial colourants (sunset yellow, tartrazine, carmoisine and ponceau 4R) or the preservative sodium benzoate, or both, exacerbated hyperactive behaviours as rated by parents. The nature of the response is individual and appears to have a pharmacological rather than an allergic mechanism.</td>
<td>Pelsser et al (2011) found that while elimination diets may assess whether ADHD is induced by food, the prescription of diets on the basis of IgG blood tests should be discouraged.</td>
<td>A literature review from 1980 through October 2011 found no studies (RCTs or cohorts) which evaluated the relationship between allergies and ADHD. The results of an RCT that examined the use of a restricted diet on the behavior of children with ADHD found that while elimination diets may assess whether ADHD is induced by food, the prescription of diets on the basis of IgG blood tests should be discouraged (Pelsser et al, 2011).</td>
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### Values and Preferences:
- Based on anecdote or inaccurate information from lay sources, patients and family members may express a range of preferences for allergy evaluation for ADHD symptoms.

### Cost (Resource Utilization):
- Low-moderate, based on insurance coverage of patient/family.

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* (Balance of Harms/Benefits, Evidence Strength, Values/Preferences, Costs)
References


(17) Strattera 10mg, 18mg, 25mg, 40mg, 60 mg or 80 mg Hard Capsules. 2008. Eli Lilly and Company Ltd. http://emc.medicines.org.uk


(54) Provigil 100 mg Tablets, Provigil 200 mg Tablets. 2008. Cephalon UK Limited. 
http://emc.medicines.org.uk


