Overview of ADHD

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Inattention

Six or more symptoms for children ≤ 16, or five or more for adolescents ≥ 17; symptoms have been present for at least 6 months, and they are inappropriate for developmental level:

- Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.
- Often has trouble holding attention on tasks or play activities.
- Often does not seem to listen when spoken to directly.
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).
- Often has trouble organizing tasks and activities.
- Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).
- Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
- Is often easily distracted
- Is often forgetful in daily activities.

Hyperactivity & Impulsivity

Six or more symptoms for children ≤ 16, or five or more for adolescents ≥ 17; symptoms have been present for at least 6 months, and they are inappropriate for developmental level:

- Often fidgets with or taps hands or feet, or squirms in seat.
- Often leaves seat in situations when remaining seated is expected.
- Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
- Often unable to play or take part in leisure activities quietly.
- Is often "on the go" acting as if "driven by a motor".
- Often talks excessively.
- Often blurts out an answer before a question has been completed.
- Often has trouble waiting his/her turn.
- Often interrupts or intrudes on others (e.g., butts into conversations or games)

Classic ADHD

Characterized by pervasive difficulties with attention, concentration, sitting still, that occur in multiple social contexts (home, school, social activities outside home & school), and is noticed in childhood (before the age of 7 in DSM-IV; symptoms present before age 12 in DSM-V).

In addition, the following conditions must be met:

- Several inattentive or hyperactive-impulsive symptoms were present [though not necessarily brought to clinical attention] before age 12 years.
- Several symptoms are present in two or more setting, (such as at home, school or work; with friends or relatives; in other activities).
- There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.
- The symptoms are not better explained by another mental disorder (such as a mood disorder, anxiety disorder, dissociative disorder, or a personality disorder). The symptoms do not happen only during the course of schizophrenia or another psychotic disorder.

Diagnostic Considerations

More likely to be diagnosed, and to be diagnosed early:

- Male sex
- Hyperactive symptoms (more common in boys)
- Competitive/well-resourced school
- Family with higher educational background / higher educational and career aspirations
- Native English speakers
- Family more familiar negotiating medical and educational bureaucracy

Screening Scales

- The Adult ADHD Self-Report Scale (ASRS) v 1.1 is useful for screening and for documenting current symptom severity.
  It is widely available online, including in self-scoring formats:
  - https://psychology-tools.com/test/adult-adhd-self-report-scale
- For children and adolescents, the Conners Comprehensive Behavior Rating Scales™ (including parent and teacher assessments) are recommended, though they are proprietary
  - https://www.wpspublish.com/conners-cbrs-conners-comprehensive-behavior-rating-scales
- Prevalence is 2-7% of children and adolescents, 3-5% of adults.

stimulants

METHYLPHENIDATE TYPE

methylphenidate IR (Ritalin®)

methylphenidate ER (Concerta®, others)

Quillivant XR (liquid ER form)

mixed IR/ER: Metadate® (30/70), etc.

Jornay PM®: super-XR methylphenidate taken at bedtime

dexmethylphenidate IR and ER (Focalin®)

AMPHETAMINE TYPE

mixed amphetamine salts IR or ER (Adderall®)

dextroamphetamine (Dexadrine®)

lisdextamfetamine (Vyvanse®)

bupropion

- Dopamine reuptake inhibitor (DRI), minimal serotonin reuptake inhibition (50:1)
- Boxed warning for seizure risk in patients with eating disorders
- Seizure risk increases slightly with IR formulation (use XL if possible!) and above 450 mg daily (check med interactions)
- Benefits also for depression (not for anxiety), smoking cessation, weight loss, possibly for stimulant use disorder
- May be most useful in patients with comorbidities

atomoxetine

- Norepinephrine reuptake inhibitor (NRI)
- Not super effective for ADHD
- No other FDA indications
- Efficacy is low
- May be most useful in patients who have contraindications to stimulants, bupropion, or α_2-agonists

α_2 agonists

GUANFACINE

XR-formulation (Intuniv®) FDA-indicated for ADHD in adolescents

IR also effective but hard to maintain BID dosing

May be especially useful for patients with anxiety or hx of substance use disorder

Sedating in the first 2 weeks

CLONIDINE

IR and CR formulations, as well as a patch

Not FDA-indicated, but data supports efficacy

Higher side effect burden than guanfacine: more sedation, more rebound hypertension

modafinil / armodafinil

- Mechanism unclear: weak dopamine reuptake inhibitor, thought to have indirect effects on orexin and histamine receptors, leading to wakefulness
- Modest benefit for ADHD
- Not FDA indicated

tricyclic antidepressants

- Some data for TCAs such as nortriptyline with strong NRI effect
- Modest benefit for ADHD
- Not FDA indicated
- Be aware that this may explain history of a better response on TCA or NRI, or could consider TCA for someone with ADHD not responding well to the other standard meds

cognitive-behavioral therapy

- Harder to access but can be helpful
- Boards answer is that stimulants are the most effective treatment, but the stimulant trials have been better funded than purely behavioral trials

other treatments / differential diagnosis

- Evaluate for sleep apnea
- Consider iron deficiency in children with low ferritin levels – rare but known and reversible cause of attentional deficits. [Konofal, Eric, et al. 2004 Iron Deficiency in Children With Attention-Deficit/Hyperactivity Disorder. Archives of Pediatrics & Adolescent Medicine 158(12):1113-1115.]
- Anxiety or depression can present as problems with attention/concentration and can interact in mutually exacerbating ways with comorbid ADHD
- It's surprisingly hard to prove an effect of sugar, caffeine, or other dietary factors – they show on parental ratings, but hard to discern with double-blinded clinician or teacher ratings

Monitoring and Safety Questions

Increasing challenge: teen or young adult presents with cannabis use, challenges in school. Says they do better on exams when they borrow a friend's Adderall

- Cardiac monitoring: not indicated for general patient. Consider if there is a significant cardiac history
- Stimulants tend to decrease appetite and therefore decrease growth in children. Consider "drug holidays". Chronic stimulant use may still reduce overall projected height by up to an inch
- Prescription stimulants and later substance misuse: kids and adults with ADHD are already at greater risk of substance use disorders. No evidence that prescription stimulants worsen this, and may help
- Importance of meeting developmental milestones
- Low self-esteem

Clinical Examples: ADHD and cannabis

Increasing challenge: teen or young adult presents with cannabis use, challenges in school. Says they do better on exams when they borrow a friend's Adderall

- Studies show that stopping cannabis improves test scores and objective performance measures while adding stimulants only improves patients' self-assessment → advise pt to stop the cannabis

Thank You

Psychopharmacology Guidelines for Primary Care: ADHD
Timothy M. Hall, MD PhD
Revision: 2021 Sep 28

I. Diagnostic Guidelines[1]

Classic ADHD is characterized by pervasive difficulties with attention, concentration, sitting still, that occur in multiple social contexts (home, school, social activities outside home & school), and is noticed in childhood (before the age of 7 in DSM-IV; symptoms present before age 12 in DSM-V, though not necessarily coming to clinical attention).

1. **"Inattention: Six or more symptoms of inattention for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level:**
    - Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.
    - Often has trouble holding attention on tasks or play activities.
    - Often does not seem to listen when spoken to directly.
    - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).
    - Often has trouble organizing tasks and activities.
    - Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).
    - Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
    - Is often easily distracted
    - Is often forgetful in daily activities.

2. **Hyperactivity and Impulsivity: Six or more symptoms of hyperactivity-impulsivity for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level:**
    - Often fidgets with or taps hands or feet, or squirms in seat.
    - Often leaves seat in situations when remaining seated is expected.
    - Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
    - Often unable to play or take part in leisure activities quietly.
    - Is often "on the go" acting as if "driven by a motor".
    - Often talks excessively.
    - Often blurts out an answer before a question has been completed.
    - Often has trouble waiting his/her turn.
    - Often interrupts or intrudes on others (e.g., butts into conversations or games)

[1] Adapted from https://www.cdc.gov/ncbddd/adhd/diagnosis.html, accessed 8/20/2019; based on American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*. Arlington, VA: American Psychiatric Association.

In addition, the following conditions must be met:

- Several inattentive or hyperactive-impulsive symptoms were present [though not necessarily brought to clinical attention] before age 12 years.
- Several symptoms are present in two or more setting, (such as at home, school or work; with friends or relatives; in other activities).
- There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.
- The symptoms are not better explained by another mental disorder (such as a mood disorder, anxiety disorder, dissociative disorder, or a personality disorder). The symptoms do not happen only during the course of schizophrenia or another psychotic disorder.

Based on the types of symptoms, three kinds (presentations) of ADHD can occur:

- *Combined Presentation*: if enough symptoms of both criteria inattention and hyperactivity-impulsivity were present for the past 6 months
- *Predominantly Inattentive Presentation*: if enough symptoms of inattention, but not hyperactivity-impulsivity, were present for the past six months
- *Predominantly Hyperactive-Impulsive Presentation*: if enough symptoms of hyperactivity-impulsivity, but not inattention, were present for the past six months."

The Adult ADHD Self-Report Scale (ASRS)[1] is useful for screening and for documenting current symptom severity. It is widely available online, including in self-scoring formats: https://psychology-tools.com/test/adult-adhd-self-report-scale

For children and adolescents, the Conners Comprehensive Behavior Rating Scales™ (including parent and teacher assessments) are recommended by the task force, though they are proprietary (https://www.mhs.com/MHS-Assessment?prodname=cbrs). The Vanderbilt scales (v1) are available for free: https://www.nichq.org/resource/nichq-vanderbilt-assessment-scales[2]

Considering ADHD first diagnosed in adulthood:

We do not think that ADHD somehow appears in adults (in the absence of a brain injury). For some of these individuals, we think that some adolescents, especially brighter than average individuals, probably were able to compensate sufficiently or were insufficiently challenged in school. They first really notice problems in college, graduate school, or the workplace, when they are presented with significantly more challenging intellectual demands and/or a need to self-organize. The inattentive type of ADHD (old-fashioned pure ADD) is more common in girls and is less commonly caught in childhood. Additionally, coming to clinical attention is strongly related to education and career goals of the parents, and competitiveness of the school system. The boy who is jumping up and down on desks in a private school with college-educated/professional parents is sent for assessment, while the girl who is daydreaming quietly at the back of the classroom in a large public school and with parents who speak ESL or who are not college-educated, is not sent for assessment.

II. Treatment Guidelines

[2] Other scales listed at: https://chadd.org/adhd-weekly/which-adhd-rating-scales-should-primary-care-physicians-use/

stimulants (methylphenidate, lisdexamfetamine, amphetamines)
atomoxetine (Strattera®) – NE reuptake inhibitor, distantly related to fluoxetine
bupropion XL (Wellbutrin®)
α_2-agonists: guanfacine (Tenex®, Intuniv®) & clonidine (approved 2010)

modafinil (Provigil®)/armodafinil (Nuvigil®) mechanism unclear; off-label use
nortriptyline (Pamelor®) off-label use in US

The Boards answer to the algorithm for treatment is stimulants, then atomoxetine, then bupropion, then α_2-agonists (guanfacine, clonidine). 2018 meta-analysis found that the mixed amphetamine salts (Adderall®-type stimulants) are more effective in adults than methylphenidate, and recommended starting with mixed amphetamine salts.[2] The key summary from the abstract states:

Findings 133 double-blind randomised controlled trials (81 in children and adolescents, 51 in adults, and one in both) were included. The analysis of efficacy closest to 12 weeks was based on 10 068 children and adolescents and 8131 adults; the analysis of tolerability was based on 11 018 children and adolescents and 5362 adults. The confidence of estimates varied from high or moderate (for some comparisons) to low or very low (for most indirect comparisons). For ADHD core symptoms rated by clinicians in children and adolescents closest to 12 weeks, all included drugs were superior to placebo (eg, SMD –1·02, 95% CI –1·19 to –0·85 for amphetamines, –0·78, –0·93 to –0·62 for methylphenidate, –0·56, –0·66 to –0·45 for atomoxetine). By contrast, for available comparisons based on teachers' ratings, only methylphenidate (SMD –0·82, 95% CI –1·16 to –0·48) and modafinil (–0·76, –1·15 to –0·37) were more efficacious than placebo. In adults (clinicians' ratings), amphetamines (SMD –0·79, 95% CI –0·99 to –0·58), methylphenidate (–0·49, –0·64 to –0·35), bupropion (–0·46, –0·85 to –0·07), and atomoxetine (–0·45, –0·58 to –0·32), but not modafinil (0·16, –0·28 to 0·59), were better than placebo. With respect to tolerability, amphetamines were inferior to placebo in both children and adolescents (odds ratio [OR] 2·30, 95% CI 1·36–3·89) and adults (3·26, 1·54–6·92); guanfacine was inferior to placebo in children and adolescents only (2·64, 1·20–5·81); and atomoxetine (2·33, 1·28–4·25), methylphenidate (2·39, 1·40–4·08), and modafinil (4·01, 1·42–11·33) were less well tolerated than placebo in adults only. In head-to-head comparisons, only differences in efficacy (clinicians' ratings) were found, favouring amphetamines over modafinil, atomoxetine, and methylphenidate in both children and adolescents (SMDs –0·46 to –0·24) and adults (–0·94 to –0·29).

In short, amphetamines are the most effective in adults and reasonably well tolerated, while methylphenidate has the best combination of efficacy and tolerability in children and adolescents.

In practice, I prefer to try guanfacine or bupropion first because of lower risk of misuse and side effects, then go to a stimulant if they don't work or symptoms appear severe. I am considering whether to change my enthusiasm for guanfacine in light of the above meta-analysis, which found it to be less effective and in children/adolescents, less well tolerated (likely due to sedation). It probably still has a role in patients with comorbid anxiety or a history of substance misuse.

Atomoxetine is rarely helpful and is often difficult to get, but may be worth trying in patients with addiction history or other contraindications for stimulants.

Guanfacine[3] can be helpful if patients have significant anxiety, as it is most likely to blunt the anxiety slightly without increasing it. Insurance may deny the extended-release version (Intuniv®). In that case, I usually try prescribing immediate-release guanfacine for a month or two and document efficacy, and also that patient is unable to adhere to BID dosing due to ADHD

[3] Guanfacine is an α_{2A}-agonist like clonidine, *not* to be confused with *guaifenesin*

symptoms. Intuniv is usually approved at that point. Typical dosing range for guanfacine is 1-4 mg BID or q day, depending on the formulation.

Most patients have some mild sedation on guanfacine for the first 1-2 weeks, so it's better to dose it at bedtime. Most patients habituate to the sedating effect within 2 weeks.

Like beta-blockers, α_{2A}-agonists have a mild anti-anxiety effect, very different from the other ADHD meds.

Bupropion is useful if there is comorbid depression, nicotine dependence, overweight, or history of stimulant use disorder. Bupropion is contraindicated (Black Box warning) in patients with history of eating disorder or seizure disorder, or at high risk for seizure.

Pediatric Guidelines: Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, Earls M, Feldman HM, Ganiats TG, Kaplanek B, Meyer B, Perrin J, Pierce K, Reiff M, Stein MT, Visser S. (2011) "ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents." *Pediatrics, 128*(5), 1007-1022. doi:10.1542/peds.2011-2654

Adult Guidelines: Post, R. E., & Kurlansik, S. L. (2012). "Diagnosis and management of adult attention-deficit/hyperactivity disorder." Am Fam Physician, 85(9), 890-896. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22612184

Prevalence is around 2-7% in children and youth.[3] Estimated rates in adults vary significantly from study to study, but often within a range of 2-5%; one recent world survey estimated an overall adult prevalence of 2.8%.[4]

Clinically, if someone presents with prior testing and a track record of doing well on a medication without suspicion of diversion or misuse, then it is generally appropriate to continue them on the medication. This is appropriately managed in a primary care setting without need for referral to psychiatry. ***Referral should be triggered by concern that the diagnosis is wrong, that there is a comorbid psychiatric problem that's not being addressed, or that there is suspicion of misuse.***

Differential diagnosis includes: other learning disorders, vision or hearing disorders in children, mood disorders, anxiety disorders, substance use disorders.

Chronic cannabis use can cause mild cognitive impairment that will not be reversed by stimulants, but will reverse with abstinence from cannabis. Occasional cannabis use, which is legal in California, should not by itself preclude treatment of ADHD that has otherwise been documented.

Algorithm for adult patient who comes requesting treatment for ADHD

If there is a prior dx of ADHD in an adult patient,
together with plausible reported history consistent with ADHD,
current sxs of ADHD as documented on Adult Self-Report Scale (ASRS) or similar,
and they are reporting FDA-indicated meds in a normal dosing range…

Then it is reasonable to run a CURES report and offer a bridge refill prescription of their current/old meds for 30 days, pending a good-faith effort to obtain documentation from their previous treating clinician. Have the patient sign an ROI for you to talk to the other clinician and have the patient attempt to get the records sent to you.

There may be good reason they are unable to obtain records, particularly if they were from student health from several years ago, or other plausible reason that prior treating clinician is unable to provide the records.

At 30-day follow-up, if the following are true, then it is reasonable to proceed with refills q 90 days:

- CURES report shows no aberrant behaviors
- Patient is not reporting AEs such as insomnia, increased anxiety, undesirable weight loss, bruxism, intolerable caffeine sensitivity, etc.
- Patient is stable on dose, with no early refills or requests to increase dose

Proposed Smartphrase for patient handout:

Establishing care at UCLA FHC for Attention Deficit Hyperactivity Disorder, also known as ADHD or ADD.

ADHD is a syndrome characterized by persistent difficulties with attention, concentration, impulsiveness, task organization, and/or sitting still. Persons with ADHD can benefit from specific skills training to improve organization and task management skills (CBT). They may also benefit from certain medications. These medications include guanfacine (brand name Tenex® for twice-daily dosing, or Intuniv® for once-daily dosing), bupropion (Wellbutrin®), or stimulants: Adderall®, Vyvanse®, Ritalin®, Concerta®, or Focalin®), or atomoxetine (Strattera).

The stimulants are all forms of amphetamine. They are all Schedule II medications, which means that they need a hard copy prescription each month, separately written on special prescription paper. Stimulants cannot be called in or faxed to a pharmacy and they cannot be written for refills.

Because stimulants are controlled substances, and because they can have potentially serious side effects (including irritability, anxiety, mood swings, disrupted sleep, weight loss, and exacerbation of heart problems), it is recommended that they be prescribed by only one clinician at a time, so that the prescribing clinician can monitor for safety and possible side effects. Once you are stable on a particular dose of a stimulant for your ADHD, your prescribing clinician will discuss with you how frequently you will need to be seen at appointments for monitoring. Depending on various factors including your health history, this may be as frequently as every month.

Because stimulants are controlled substances, it is not usually possible to have them filled by someone other than the primary prescriber. Because they require a hard copy prescription, you will need to notify your physician several days in advance of needing a refill, so that they will

have time to write the prescription and leave it at FHC for you to pick up. Please be aware of this potential time delay around holidays, or if your primary physician is only at FHC certain days of the week, as it is usually not possible for another physician to prescribe refills.

If you are requesting that we take over prescribing your ADHD medication from a previous clinician, we will need certain documentation in order to provide you with medically appropriate care. We are requesting the following information:
• your previous dose of your ADHD medication
• other medications that have been tried in the past and whether they were helpful or not
• results of any formal neuropsychological testing that may have been done.
• a Release of Information form allowing us to discuss your history with your previous prescribing clinician.

If your dose of ADHD medications is at or above the high-end of FDA recommendations, we may require that you have an evaluation by a psychiatrist or neuropsychologist, or that you provide us with documentation from your previous physician explaining the rationale for this higher dose. We are not able to provide you with more than a one month supply of ADHD medications without receiving this documentation or communication from your prior provider. Thank you for understanding.

References:

1. Kessler RC, Adler L, Ames M, et al. The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychol Med.* 2005;35(2):245-256.
2. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry.* 2018;5(9):727-738.
3. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry.* 2018;5(2):175-186.
4. Fayyad J, Sampson NA, Hwang I, et al. The descriptive epidemiology of DSM-IV Adult ADHD in the World Health Organization World Mental Health Surveys. *Atten Defic Hyperact Disord.* 2017;9(1):47-65.