

Adult Attention Deficit/Hyperactivity Disorder (ADHD): Comorbidities and Impact on Treatment

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Disclosure

- I have no actual or potential conflict of interest in relation to this activity.
- I do plan on discussing unlabeled or investigational uses of a commercial product.

The goal of this presentation is to provide information regarding the treatment of ADHD in the adult population. Attention will be made to addressing the impact of comorbidities on the diagnosis and pharmacotherapeutic decisions.

Objectives.

By the end of this presentation the participant should be able to:

- list the signs and symptoms of ADHD in adults,
- define appropriate goals of pharmacologic therapy in adults with ADHD,
- determine the effect of comorbidities on pharmacotherapy decisions, and
- create public health policy that promotes effective management of adult adhd.

Attention-Deficit/Hyperactivity Disorder (ADHD)

- First described in 1902 by George Still-a defect that affected inhibitory volition.
 - Many literary notations back to the 1500s.
 - Official diagnosis with DSM-II.

Diagnostic and Statistical Manual 5th edition.

- Criteria A1 and A2, B, C, D, E
- Criteria A1-Inattention: 6 or more of the following and have persisted for more than 6 months. Different than others at that developmental stage and associated with negative consequences.

Inattention (6 or more)

- Makes careless mistakes and fails to give details on work.
- Difficulty sustaining focus and attention.
- Appears not to listen when spoken to.
- Does not follow through with instructions.
- Poor organization skills.
- Avoids tasks requiring sustained mental effort.
- Often loses things.
- Easily distracted by nearby stimuli.
- Forgetful in daily activities.

Criteria A2

Criteria A 2: hyperactivity and impulsivity-

- 6 or more of the following symptoms for at least 6 months that is inconsistent with developmental level and negatively impacts social and academic/occupational activities.

Hyperactivity and impulsivity (6 or more)

- Often fidgets or squirms in seat.
- Leaves seat when sitting is expected.
- Runs and climbs when it is inappropriate.
- Unable to play in leisure activities quietly.
- Appears ‘on the go’ and ‘driven by a motor.’
- Talks excessively.
- Blurts out an answer before a question is completed.
- Has difficulty waiting for his turn.
- Interrupts or intrudes on others.

Criteria A, B, C, D, E

Criteria B-

- Several symptoms were present prior to age 12.

Criteria C-

- Some impairment from the symptoms must be present in at least two settings (e.g., at home and at school or work)

Criteria A, B, C, D, E

Criteria D

- There must be clear evidence of interference or quality reduction of developmentally appropriate social, academic, or occupational functioning.

Criteria E

- The disturbance does not occur exclusively during the course of other mental disorders

ADHD specifiers

- Predominantly Inattentive Presentation
- Predominantly Hyperactive/Impulsive Presentation
- Combined Presentation

Current severity level

- Mild
- Moderate
- Severe

Not quite full symptom display

- Other Specified-explains what is missing
- Unspecified-does not explain what is missing

Adult ADHD self-report scale (ASRS)

- 18 questions
- Never, rarely, sometimes, often, very often
- Part A (q 1-6) shows likelihood of having adult ADHD
- Part B (q 7-18) reflects areas of impairment and concern per the patient. (QOL effects)

2. How often do you have trouble getting things in order when you have to do a task that requires organization?
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?
7. How often do you make careless mistakes when you have to work on a boring or difficult project?
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?

Prevalence rates

- 8.7% in children
- 4.4% in adults
 - 40-65% will continue with symptoms into adulthood.
 - Severity of symptoms seems to decline.
- Rates similar in Europe.

Larson K, et al. Pediatrics. 2011. Kaplan G, Newcorn JH. Pediatric Clinics of N. Amer. 2011.
CDC.gov. Geissler J, et al. Exp Rev Neurotherapeutics. 2011.

Causes

- Genetics

- family studies, twin studies, adoption studies have all shown a genetic link.
 - Adoption studies show linkage to biological relatives.
- Likely that multiple DA and NE related genes are involved.
- ADHD in 1st degree relatives is 4-10x greater with prevalence 20-50%.

Adler LA, et al. J of ADHD and Related Disorders. 2009.
Shaw P, et al. Proc Natural Acad of Sciences. 2007.
Geissler J, et al. Exp Rev Neurotherapeutics. 2011.

Delayed brain maturation

In ADHD subjects compared to controls:

- Cortical thickness is delayed.
- Cortical surface area is delayed.

- Approximately a 2-3 year delay in children.
- Near 18 yo the differences are no longer significant.
 - May explain why many children with ADHD no longer are diagnosable by late adolescence.

Shaw P, et al. Proc Natl Acad Sci USA. 2007.

Shaw P, et al. Biol Psychiatry. 2012.

Neurobiology

- Blocking NE alpha2 receptors results in ADHD like behavior.
- Dysfunction in prefrontal-striatal neural circuits
 - Reductions in synaptic DA, due to enhanced DA reuptake and increased catabolism.
- P50 suppression deficiency.
 - Deficiency in the ability to suppress reaction to an auditory stimuli.
- Delayed brain maturation.

Arnsten AFT. CNS Drugs. 2009. Holstein DH, et al. Psychiatry Research. 2013.

Geissler J, et al. Exp Rev Neurotherapeutics. 2011. Spencer TJ. CNS Drugs. 2009.

Volkow ND, et al. Biol Psychiatry. 2005. Krause EH, et al. Neuroscience Behav Rev. 2003.

Health System Cost

- Health care costs are increased in ADHD adults compared to non ADHD controls.
 - Increased comorbidities which impacts overall healthcare costs.
- ADHD positive workers have 5% reduction in performance, double the sick days and workplace accidents (manufacturing).
- Cost of treating adults with comorbid depression and ADD v only depression is 29% higher.
- Family cost increases of children with ADHD related to education and healthcare.

Secnik K, et al. Pharmacoeconomics. 2005. Biederman J, et al. J Clin Psychiatry. 2012. Kessler RC, et al. Psychological Med.2009. Fishman PA, et al. J Clin Psych. 2007. Doshi JA, et al. JAACAP. 2012

Patient cost

- Lower educational grade attainment.
 - Lower occupational grade.
 - Lower earnings on average.
- Adults have negative perceptions of impact of ADHD on daily life and social relationships.
- Increased criminality.
 - Criminality declines during periods of treatment in adults.
 - Stimulants have a slight advantage over non stimulants.

Galera C, et al. Br J Psychiatry. 2012. Knapp M, et al. J of MH Policy and Economics. 2011. Doshi JA, et al. JAACAP. 2012. Brod M, et al. Health and Qual Life Out. 2012. Lichtenstein P, et al. NEJM. 2012.

Driving with adult adhd

- ADHD adolescents and adults have increased:
 - Accidents
 - Driving violations
 - License suspensions
- Treatment with stimulants and atomoxetine show improved driving performance which correlated with reductions in ADHD symptoms.

Jerome L, et al. J Can Acad Child Adol Psychiatry. 2006.

Sobanski E, et al. European Psychiatry. 2013. Cox DJ, et al. Pediatrics. 2006.

Pharmacotherapy

- stimulants (amphetamines, methylphenidate)-FDA approval
- atomoxetine-FDA approval
- guanfacine
 - clonidine
- bupropion
- venlafaxine
- modafinil
- tricyclic antidepressants
- duloxetine

Comorbidities

- Lifetime comorbidity of another psychiatric disorder is 75% compared to 45% in controls.
 - Primarily mood, anxiety and substance use.
 - Psychiatric comorbidity as a child increases risk of ADHD persistency into adulthood.
- Worsening functioning on most social domains.
 - Correlates with lower socioeconomic status as an adult.
- Increased muscle tone.
 - Resulting in increased pain as adult.
- Increased mortality from suicide.

Ferrin M, et al. Future Neurology. 2011. Larson K, et al. Pediatrics. 2011.

Fried R, et al. J of ADHD and Related Disorders. 2009. Kooij SJJ, et al. BMC Psychiatry. 2010.

Biederman J, et al. J Psychiatric Research. 2011. Stray LL, et al. Beh Brain Functions. 2013.

Kessler RC, et al. Am J Psychiatry. 2006. Reinhardt MC, et al. J Pediatr. 2013. Barbaresi WJ, et al. Pediatrics. 2013.

Comorbidities

Major Depressive Disorder

Bipolar Disorder

Substance Use Disorder

Major Depressive Disorder - MDD

- 18.6 % of those with ADHD also have MDD compared to 7.8% without.
- 9.4% of those with MDD also have ADHD.
- Severity of depression pos. correlated to severity of ADHD.
- Treat the MDD before addressing ADHD.
 - if mild depression then treat ADHD first and assess if the depression remits.

Kessler RC. Am J Psychiatry. 2006. Kooij SJJ. BMC Psychiatry. 2010. Simon V. Eur Psychiatry. 2013.

MDD

- Some antidepressants are effective at treating ADHD in patients devoid of MDD.
 - Bupropion
 - venlafaxine, duloxetine, TCAs
- Combination SSRI antidepressant for MDD and a stimulant is acceptable.

Maneeton N. Psychiatry Clin Neurosciences. 2011. Wilens TE. Biol Psychiatry. 2005. Kuperman S. Ann Clin Psychiatry. 2001. Amiri S. Hum Psychopharmacol Clin Exp. 2012

Bipolar Disorder

- 19.4% of those with ADHD also have bipolar disorder (v 3.1% without).
- 21.2% of bipolar patients also have ADHD.
- Always treat bipolar first then reassess level of ADHD severity.
- Response to mood stabilizer is not changed if patient has comorbid ADHD

Kessler RC. Am J Psychiatry. 2006. Kooij SJJ. BMC Psychiatry. 2010. State RC. J Clin Psychiatry. 2004.

Bipolar Disorder

- Possible to assess for both ADHD and bipolar
 - unless patient is currently in a manic or depressed episode.
- ADHD treatment can be with stimulants- does not seem to worsen mania frequency.
- Atomoxetine is mania-switch safe and also safe for:
 - Substance use disorder, common in this population
 - Will not worsen psychosis if patient in a current episode (unlike stimulants)
- Bupropion is mania-switch safe antidepressant
 - SNRIs may cause switching.
- Alpha2 agonists are safe in bipolar but not studied specifically for ADHD symptoms.

Scheffer RE Am J Psychiatry. 2005. Wilens TE. Biol Psychiatry. 2003. Lydon E. J Clin Psychopharmacology. 2006.

Substance Use Disorder

- 15.2% of those with ADHD also have a substance use disorder (v 5.6% without).
- 10.8% of substance use disorder patients also have ADHD.
- Stimulant misuse frequently occurs in college settings.
 - average in past year of 4.1% (range 0-25%)

Kessler RC. Am J Psychiatry. 2006. McCabe. Addiction. 2005.

Substance Use Disorder

- Severity of EtOH use correlated with severity of ADHD.
 - Particularly inattentiveness and non-planning impulsiveness
- In 15-17 yo: diagnosis of ADHD correlated with increased EtOh.
 - Other age groups were similar to controls.

Bozkurt M, et al. Neuropsychiatric Dis and Treatment. 2016. Molina BSG, et al. Alc: Clin and Exp Res. 2007.

Stimulant use for ADHD and risk of abuse

- The speed with which DA is increased in the brain is the key risk for abuse. Absolute DA increases are less relevant.
 - Intravenous and inhalation are fastest.
- Adults with comorbid substance use disorders have low rates of study stimulant abuse in trial data.
 - Treating the ADHD does not correlate with a lowering of substance use.
 - But does not result in increased substance misuse either.
- Stimulants likely to help the ADHD symptoms but unlikely to change substance use.

Schubiner H. CNS Drugs. 2005. Swanson JM, et al. Neuroscience and Biobehavioral Rev. Volkow ND, et al. Am J Psychiatry. 2003. Humphreys KL, et al. JAMA Psychiatry. 2013.

Substance Use Disorder

- Must assess risk of patient misuse or patient diversion before starting stimulant.
 - Stimulants in non sub. use dis. adults not a risk factor for inducing a sub. use disorder.
- Atomoxetine is first line in substance use disorder adults.

BAP ADHD Guideline. 2014. Ramos-Quiroga, JA. Curr Med Res Op. 2013.

Expert Consensus regarding substance use and adult ADHD

- Treat substance use disorder concurrently.
- The transdermal methylphenidate and lisdexamfetamine may have less abuse potential but can still be used to induce a euphoria.
- Long acting stimulants are safer than short acting.
- Be vigilant regarding diversion or misuse.

Upadhyaya HP. J Clin Psychiatry. 2007.

Short v long acting stimulants

- Long acting likely to have a lower abuse risk.
- Long acting more useful if chronically used and needed throughout the day.
- Short acting useful if needed for specific events.
 - Studying for a test, preparing proposal for work, etc.
- Meta-analysis showed better efficacy with short acting.
 - Experts recommend long acting as first choice.

Peterson K, et al. *Psychopharmacology*. 2008. Ramos-Quiroga JA, et al. *Current Med Res Op*. 2013.
Kooij SJJ, et al. *BMC Psychiatry*. 2010. Nutt DJ, et al. *J Psychopharmacology*. 2007. CADDRA. 2009.

Stimulant diversion

- High rates of intermittent misuse in academic environments (16-22%).
 - More competitive schools have higher misuse rates.
 - Most common reason is for performance enhancement.
 - Second most common reason is for recreation.
- The intermittent diversion of stimulants may be as high as 35% in college students with a valid prescription.

Upadhyaya HP. J Clin Psychiatry. 2007. McCabe SE, et al. Addiction. 2005.
Teter CJ, et al. J Am Coll Health. 2005. Babcock Q, et al. J Am Coll Health. 2000.
Schubiner H. CNS Drugs. 2005.

Adult ADHD Conclusion

- Harder to diagnose due to:
 - reduced intensity of symptoms
 - multiple comorbidities.
- Treat all other factors that can worsen attention.
 - Pain, anxiety, depression, sleep disorders, adjustment disorders, medications, etc.
- Apply non pharmacologic interventions first
 - Initiate necessary pharmacotherapy.

Adler LA, et al. J Clin Psychiatry. 2008. Nutt DJ, et al. J Psychopharmacology. 2006.

Kooij SJJ, et al. BMJ Psychiatry. 2010 . Antai-Otong D. Perspectives in Psychiatric Care. 2008.

Ramos-Quiroga JA, et al. Current Med Res Op. 2013.

Drug selection for Adult ADHD

- Stimulants work better than non stimulants (as in children) on core ADHD symptoms.
- Methylphenidate IR was better than longer acting stimulants and bupropion.
 - Long acting still recommended as more practical option.
- Venlafaxine, TCAs and other SNRIs are legitimate first choices due to frequent comorbidities of anxiety, depression.
 - Atomoxetine may be better than stimulants for anxiety.
 - Bupropion helpful in depression but not anxiety.
- Modafinil has positive results for ADHD symptoms.
- Comorbidity must be assessed.

Secnik K, et al. Pharmacoeconomics. 2005. Ramos-Quiroga JA, et al. Current Med Res Op. 2013.
Kooij SJJ, et al. BMJ Psychiatry. 2010. Nutt DJ, et al. J Psychopharmacology. 2006.
Peterson K, et al. Psychopharmacology. 2008. BAP ADHD Guideline. 2014.

Summary

- Depression comorbidity:
 - venlafaxine, bupropion best first choices
 - TCAs effective, tolerability and safety limit their use
 - Other SNRIs helpful for depression
 - Questionable efficacy for ADHD symptoms
 - Levomilnacipran?
 - Attention in depression improves but it does with all meds that treat depressive symptoms

Ramos-Quiroga JA, et al. Current Med Res Op. 2013. Kooij SJJ, et al. BMJ Psychiatry. 2010. BAP ADHD Guideline. 2014.

Summary

- Bipolar comorbidity
 - ADHD possible but hypomania symptoms make diagnosis difficult
 - Effective treatment of bipolar symptoms is primary goal
 - Atomoxetine and bupropion safe and effective
 - Stimulants effective
 - Seemingly safe regarding mania switching
 - Potential for psychosis if patient currently manic
 - High levels of substance use in this population make this a limited option
 - May result in decreased efficacy when given with an antipsychotic class mood stabilizer.

Wozniak J. Psychiatry Times. 2011. Nutt DJ. BAP Guideline for Adolescents and Adults. 2006.

summary

- Substance use disorder
 - Stimulants not recommended despite efficacy
 - Must also consider risk of diversion
- Atomoxetine first choice
 - Unfortunately, has minimal effect at reducing substance use rates
- Alpha 2 agonists, bupropion and modafinil potential options but with limited data.

Nutt DJ. BAP Guideline for Adolescents and Adults. 2006. Ramos-Quiroga JA, et al. Current Med Res Op. 2013. Kooij SJJ, et al. BMJ Psychiatry. 2010.

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