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Review Article

Pharmacotherapeutic options for attention deficit hyperactivity disorder (ADHD)

Jarnail Singh*

Department of Pharmacology, Pt. BD Sharma UHS, Rohtak, Harayana, India

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***Correspondence:**
Dr. Jarnail Singh,
E-mail: drjarnail@gmail.com

ABSTRACT

Attention deficit hyperactivity disorder (ADHD), the most common behavioral disorder in children, may disable the patient throughout life. Diagnosis of ADHD is based on DSM-IV-revised criteria. ADHD is a costly health problem and various drugs including stimulants, tricyclic antidepressants (TCAs), bupropion, pemoline, clonidine and atomoxetine have been used to treat it. Atomoxetine and stimulants are the most commonly prescribed drugs for pediatric ADHD with similar efficacy, but serious adverse events with atomoxetine have been reported.

Keywords: Attention deficit hyperactivity disorder, ADHD, ADR, Stimulants, TCAs

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a behavioral disorder, most commonly diagnosed in children and adolescents. It affects 8-10% of school age children; and boys are more commonly effected than girls.[1] According to CDC approximately 11% of children aged 4-17 have been diagnosed as ADHD as per report 2011-12.[2]

Diagnosis of ADHD is based upon identification of specific behaviors obtained from the parent, teacher, and patient that meet DSM-IV-Revised criteria.[3] Genetic factors, extremely low birth weight and environmental conditions such as head trauma are important in etiopathology of ADHD.[4,5] Symptoms and problems of ADHD can persist throughout the life of the patient.[6]

In children ADHD is a costly health problem. Drug treatment, though not as effective as in combination with behavioral treatment, is likely to be more cost effective in treatment of children with ADHD, especially those without co-morbid disorders.[7]

Amphetamines have been in use in the treatment of ADHD since last 50 years; and other drugs such as tricyclic antidepressants (imipramine and desipramine), bupropion, pemoline, 3rd generation antidepressant venlafaxine, selegiline and alpha-2 agonists (clonidine and gaunfacine) also have been tried.[8]

Commonly used drugs for treating ADHD in children are stimulants (methylphenidate, amphetamine and methamphetamine), bupropion and atomoxetine (Table 1).[9] Atomoxetine is currently the most commonly prescribed drug for pediatric ADHD, but serious ADRs have been reported including psychosis or mania, aggression, suicidality, severe liver injury, seizures, prolonged QTc with over dose, and tics.[8]

STIMULANTS

Stimulant is the most common medication used for treating ADHD, although it actually has a calming effect on children with ADHD. Many types of stimulant medications are available. (Table 2).

Table 1: Current pharmacotherapy of ADHD.

Drug group/drug	Mechanism of action	Remarks
Psychostimulants: (amphetamine, dextroamphetamine, methylphenidate, Dexmethylphenidate, lisdexamfetamine)	Block uptake and increase release of DA and NE into extraneuronal space.	Improvement in behavior in 70-80% of children [8], discontinuation of drug treatment because of ADR in 1-4% of children.[10] Methylphenidate transdermal patch has been approved by FDA for OD application.
Atomoxetine	Non-stimulant, SNRI	Standard drug in ADHD, better tolerated (compared with methylphenidate), 25-30% or more improvement in symptoms by 6-12 week treatment in ADHD children.[11]
Alpha-2 selective adrenergic agonists (Gaunfacine, clonidine)	Gaunfacine is longer acting and more specific alpha-2 agonist.[12]	Not often used in treatment of ADHD because of cardiac side effects and availability of safe and effective drugs.[7] These agents are last-step alternatives in the management of ADHD.
TCAs (imipramine, desipramine, nortriptyline)	Inhibit reuptake of NE or 5-HT at presynaptic neuron.	Not frequently used in treatment of ADHD because safe drugs are available.[7]
Venlafaxine	Venlafaxine and its metabolite ODV are equipotent SNRI.	Preliminary studies and case series relevant to treatment of ADHD.
Selegiline	Irreversible inhibitor of MAO-B, and DA and PEA levels are raised, also metabolized to amphetamine and methamphetamine.	It may have additional therapeutic neurotransmitter effects.
Pemoline	Similar to stimulants.	Not recommended because of liver toxicity.[7]
Bupropion	Inhibition of uptake of DA, 5-HT, NE	Not approved by FDA for use in children.[7] Treatment effect is smaller, and ADR are more comparison to methylphenidate.[13]

NE=Norepinephrine, SNRI=Selective NE reuptake inhibitor, DA=Dopamine, PEA=Phenylethylamine, ODV=O-desmethylvenlafaxine, TCA=Tricyclic antidepressants, MAO-B=Monoamine oxidase-B, FDA=US Food and drug administration.

Table 2: First-line drug therapy for ADHD.[14]

Stimulants: short acting (IR)	Onset of action (min)	Duration of effect on behavior (hrs)
Methylphenidate	20-30	3-6
Dexmethylphenidate	30	3-6
Mixed amphetamine salts	30	5-7
Dextroamphetamine	20-60	4-6
Stimulants: intermediate acting (SR/ER)		
Methylphenidate IR*	60-90	3-8
Dextroamphetamine	60-90	6-10
Stimulants: long acting (once daily)		
Methlphenidate	1.8 hr	7-9
Dexmethylphenidate	30	12
Lisdexamfetamine dimesylate*	2 hrs	10
Mixed amphetamine	30	8
Non-stimulant		
Atomoxetine	Slow onset	24

IR=Immediate-release, SR=Sustained-release, ER=Extended release

Few non-stimulants work differently than stimulants. In many children, ADHD medications reduce hyperactivity and improve impulsivity and improve their ability to focus, work and learn. ADHD medication may also improve physical coordination. In adults with ADHD treatment includes a combination of medication and non-medication (psycho-social) interventions. The combination of treatments is considered to be most effective in adults with ADHD. Medication alone is insufficient for treating adults with ADHD as they may

need to learn specific skills in areas like management, organization, task completion to improve their lives.[15]

Table 3: Second line drugs for treatment of ADHD.[14]

Medication	Indication
Bupropion	ADHD with intolerance to stimulants.
Clonidine	ADHD+Tics, ADHD+PTSD, Insomnia, Hyper-arousal, Aggression.
Gaunfacine	ADHD+Tics, ADHD+PTSD, PTSD, Insomnia, Hyper-arousal, Aggression, Oppositinality.
Sometimes antipsychotic medications are used to augment treatment of ADHD	
Risperidone	ADHD+Tics, ADHD+Aggression, ADHD+ Mood swings, ADHD+Severe insomnia.
Trazodone	ADHD+ Insomnia, ADHD+ Hyperactivity and or aggression.

PTSD=Post-traumatic stress disorder.

First non-stimulant ADHD medication, atomoxetine, was FDA approved for adults in 2002. Stimulants followed with mixed amphetamine salts FDA approved in 2004, dexmethylphenidate approved in 2005, and lisdexamfetamine and OROS methylphenidate approved in 2008 for adults with ADHD.[16]

MECHANISM OF ACTION ADHD MEDICATION

ADHD medication is thought to effect certain brain neurotransmitters which facilitate the transmission of messages from on neuron to other. Dopamine (DA) and norepinephrine (NE) are thought to regulate attention and behavior in patients with ADHD. Exact role of each neurotransmitter in development of ADHD symptoms is not known, but by altering the action of these neurotransmitters symptoms of ADHD can be modified.[17]

Methylphenidate and amphetamine are the most commonly used medications for treatment of adults with ADHD. Being stimulants, they block DA and NE reuptake in certain parts of brain and thus DA and NE are available in synapse to facilitate brain functioning. Also, amphetamine causes the neuron to release to release more neurotransmitters from the presynaptic neuron. While stimulants have been widely studied and prescribed for treatment of ADHD in children and adults, many adults with ADHD can also benefit from atomoxetine. Atomoxetine primarily affects neurotransmitter NE and it is a NE reuptake inhibitor. Atomoxetine also boosts action of DA.[15]

WHY TO TREAT ADHD SYMPTOMS

ADHD symptoms are not directly life threatening. Adults with ADHD may prefer psychosocial treatments i.e. self-help, counseling, coaching, working with tutors, professional organizers etc. Such psychosocial treatments may reduce need for ADHD medication. For those who regard ADHD as a biological disorder use of medicine to improve brain function makes a sense. There are a large number of research studies pointing to effectiveness and safety of ADHD medications in children and adolescents, fewer studies of medication use in adults with ADHD.[15]

WHAT TO CHOOSE: STIMULANT OR NON-STIMULANT?

Stimulants have been used for over 70 years for children with ADHD. They are highly effective, good safety and tolerability profile, and their effect can be seen within hours or days of administration. Long- acting (8-12 h) stimulants help the patient throughout the day and into the evening.[15]

Non-stimulant, atomoxetine, may be chosen to treat an adult ADHD patient if there is inadequate response to stimulants, and intolerable ADR to stimulant medication (i.e. sleep problems, loss of appetite, irritability, etc). A non-stimulant medication no risk of misuse, abuse or diversion, and also atomoxetine has the advantage of being longer acting than even the long-acting stimulants.[18] There is no scientific evidence suggesting that methylphenidate will work better than amphetamine or vice versa. Both methylphenidate and amphetamine affect DA and NE, but somewhat differently thereby individuals respond differently to each of them.[17] Modafinil works in ADHD but at a higher dose than typically used for fatigue. Modafinil improved ADHD symptoms more than placebo, and the response rate based on CGI scale was 48% for modafinil and 17% for placebo. Insomnia, headache and decreased appetite were common side effects.[19] In adults, modafinil (mean 206.8 mg/day) was as effective as dextroamphetamine (mean 21.8 mg/day) and both were better than placebo.[20] Alpha-2 agonists such as clonidine or gaunfacine have been used to treat ADHD either alone or in combination with stimulants. In a 2002 study, clonidine has been shown to be more effective than placebo in children with ADHD and Tourrette's syndrome.[21]

LONG-ACTING VS SHORT-ACTING STIMULANTS

Only long-acting stimulants are FDA approved for adults with ADHD. Long-acting stimulants last 8h or more and deliver a constant pattern of symptom relief throughout the day. Short-acting stimulants act for only 3-4 h and require more once daily dosing for most people with ADHD. Thus long-acting stimulants promote better compliance in the patients.[15]

STIMULANTS AND SUBSTANCE ABUSE

No evidence suggests that stimulant use increases chances of substance abuse or dependence in a person. Rather studies indicate that stimulant use in successful treatment in adults with ADHD can reduce chances of

substance use disorder in comparison to adults not treated for ADHD.[22]

ADHD DRUG SIDE EFFECTS

Most of the ADHD drug side effect are minor and don't result in stopping the drug. They may be alleviated by lowering the dosage, but consulting the prescribing physician is needed before changing the dosage. For most of the ADHD drugs commonly observed side effects are: decreased appetite, insomnia (may be relieved by taking the drug early in the day or adding an antidepressant), mild stomachache or headache, increased irritability or anxiety, and ticks (very rare).

These drugs control ADHD symptoms on the day they are taken and the disorder is not actually cured. The drugs enable the child to use their skills more easily, and an effort is still needed to improve schoolwork or knowledge in other other areas. ADHD drugs can help a child focus and improve behavior in many settings. They may also reduce or avoid emotional problems or addictions. Children, 4 out of 5, will still need medication as teenagers, and over half as adults.

Children who also have bipolar disorder and on lithium or valproic acid treatment may not be suitable for ADHD medication as well.

ADRS OF ADHD MEDICATION IN ADULTS

Common side effects of stimulants are decreased appetite, headache, stomachache, weight loss, dry mouth, nervousness, mood swings, dizziness, fast heart-beat. Stimulants can cause agitation thus not indicated for persons who are highly anxious, agitated for suffer from psychosis.[17] Stimulants can cause small increase in blood pressure. Patients with narrow angle glaucoma should avoid stimulants, also stimulants may worsen symptoms in patients with Tourette's syndrome or a history of ticks.

Common side effects of non-stimulant atomoxetine, are constipation, dry mouth, fatigue, insomnia, decreased appetite, erectile dysfunction, urinary hesitation/urinary retention/dysuria, dysmenorrhea, and hot flushes. Atomoxetine may cause sedation thus sometimes prescribed to be taken in evening. Mild increase in blood pressure have been reported and BP and pulse should be monitored. Gastrointestinal complaints may occur but decline within first week of treatment particularly if atomoxetine is taken with meals to avoid nausea. Patients with pre-existing heart disease or cardiac abnormalities, hypertension or hypotension or liver disease should avoid atomoxetine. Rarely, atomoxetine can cause an allergic reaction such as a skin rash.[15]

MONITORING ADHD MEDICATION

ADHD medication should be monitored for effectiveness over time. Some patients may experience unhealthy ADRs that will require a change in administration, dosing or medication. ADHD rating scale may be useful to monitor the effects of medication on core symptoms of inattention, hyperactivity or impulsivity. With careful monitoring, communication and fine tuning over time optimal results generally occur.[15]

NON-MEDICAL TREATMENTS

Medication alone is not sufficient to treat ADHD symptoms in adults, if symptoms are severe causing serious impairment in daily functioning. ADHD medication may offer improvement in core symptoms but not satisfactory improvement in areas i.e. time management, organization, planning, task completion, anger management, etc. Thus, many adults with ADHD seek further assistance in the form of psycho-social treatment i.e. cognitive behavioral therapy (CBT), time management, coaching, social skill training, money management, relationship counseling, vocational counseling and self-education about ADHD.[23]

Behavioral psychotherapy is effective when used in combination with effective ADHD medication. Metacognitive therapy has been proven to be more effective that supportive interventions and is a viable therapeutic approach.[24] Effective psycho-social treatments include behavioral parent training (BPT) and behavioral classroom management (BCM) which are best combined with the psycho-pharmacological approaches.[25] Intense exercise has a beneficial effect on children with ADHD. It can improve their attention and may help their school performance.[26]

ADHD MEDICATION AND PSYCHIATRIC CO-MORBIDITY

Adults with ADHD can have co-existing generalized anxiety disorder, social phobia, major depressive disorder, bipolar disorder, substance abuse, personality disorder or other psychiatric disorders. There are less guidelines for adults with ADHD and co-morbidities and none of the FDA approved ADHD medications are approved for treating these other conditions. Mostly co-existing conditions are treated first, before ADHD, especially if they are causing great impairment and unhappiness. Medications used to treat one condition may improve or worsen symptoms of the other condition.[15] Bupropion is a non-stimulant that addresses many conditions co-existing with ADHD. Bupropion may increase cognitive functioning and reduce depression, aggression, and hyperactivity in adults with ADHD.[27] Divalproex has been shown to reduce aggressive behavior in children with ADHD but a larger trial is needed in this regard.[28]

CONCLUSION

The therapeutic approach to ADHD has been shifting. For adults with ADHD stimulants represent the best first-

line therapeutic option. For social skills and academic performance medications combined with behavioral treatments may be indicated.

Atomoxetine has become a 2nd line because overall efffect of atomoxetine has not been as extensive as reported with stimulants. Modafinil is effective in children with ADHD as 3rd line of 4th line treatment. Clonidine and gaunfacine have mixed efficacy in ADHD but sudden deaths have been reported in children taking clonidine and methylphenidate.

Also, divalproex reduces aggressive behavior in children with ADHD, but a larger trial is needed in this regard.

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REFERENCES

1. American academy of pediatrics. Clinical practice guideline: Diagnosis and evaluation of the child with attention-deficit-hyperactivity-disorder. Pediatrics. 2000;105:1158-70.
2. Attention-deficit/hyperactivity disorder (ADHD). Availabe at http://www.cdc.gov/ncbddd/adhd/data.html
3. American psychiatric association. Diagnostic and statistical manual of mental disorders, 4th ed. rev (DSM-IV-R). Washington DC; 2000.
4. Hille ET, den Quaden AL, Saigal S, Wolke D, Lambert M, Whitaker A, et al. Behavioral problems in children who weigh 1000 g or less at birth in four countries. Lancet. 2001;357:1641-3.
5. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, et al. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit-hyperactivity disorder. JAMA. 2002;288:1740-8.
6. Biederman J. Attention-deficit-hyperactivity disorder: A life span perspective. J Clin Psychiatr. 1998;59:4-16.
7. Jensen PS, Garcia JA, Glied S, Crowe M, Foster M, Schalender M, et al. Cost-effectiveness of ADHD treatments: Findings from the multimodal treatment study of children with ADHD. Am J Psychiatr. 2005;162:1628-36.
8. Rappley MD. Attention deficit-hyperactivity disorder. N Engl J Med. 2005;352:165-73.
9. Greydanus DE, Pratt HD, Sloane MA, Pappley MD. Attention-deficit-hyperactivity disorder in children and adolescents: interventions for a complex costly clinical conundrum. Paediatr Clin N Am. 2003; 50:1049-92.
10. Efron D, Jarman F, Barker M. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder: A double-blind, crossover trial. Pediatr. 1997;100:662-6.
11. Kelsey DK, Sumner CR, Casat CD, Coury DL, Quintana H, Saylor KE, et al. Once daily atomoxetine treatment for children with attention-deficit/hyperactivity disorder; including an assessment of evening and morning behavior: A double blind, placebo-controlled trial. Pediatr. 2004;114:e1-8.
12. Horrigan JP, Barnhill LJ. Gaunfacine for treatment of attention-deficit hyperactivity disorder in boys. J Child Adolesc Pharmacol. 1995;5:215-23.
13. Barrickman LL, Perry PJ, Allen AJ, Kuperman S, Arndt Smith, Hermann KJ, et al. Bupropion versus methylphenidate in treatment of attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatr. 1995;34:649-57.
14. UMHS Attention deficit disorder guideline; 2013. Available at: www.med.umich.edu/1info/FHP/practiceguides/adhd/adhd.pdf
15. National Association for Continuing Education. Facts about approved medications for adults with ADHD. Available at www.naceonline.com/AdultADHDtoolkit/patienteducation/medications.pdf
16. Goodman DW. The black book of ADHD. MBL Communications, Inc; 2009.
17. Barkley RA. Attention deficit hyperactivity disorder in adults: The latest assessment and treatment strategies. Boston: Jones and Bartlett Publishers; 2010.
18. Joel L. Young ADHD grown up: A guide to adolescent and adult ADHD. New York: WW Norton & Company; 2007.
19. Biederman J. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double blind, placebo-controlled, flexible-dose study. Pediatr. 2005;116:e777-84.
20. Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. J Child Psychopharmacol. 2000;10(4):311-20.
21. Tourrette syndrome study group. Treatment of ADHD in children with tics: a randomised controlled trial. Neurol. 2002;58(4):527-36.
22. Biederman J, Willens T, Mick E, Spencer T and Faraone S. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk of substance use disorder. Pediatr. 1999;104:e20.
23. Ramsay JR, Rostain AL. Cognitive behavioral therapy for adult ADHD: An integrative psychosocial and medical approach. New York: Routledge, Taylor and Francis Group; 2008
24. Solanto MV, Marks DJ, Wasserstein J, Mitchell K, Abikoff H, Alvir JM, et al. Efficacy of Meta-Cognitive Therapy for Adult ADHD. Am J Psychiatr. 2010;167(8):958-68.
25. Pelham WE, Fabiano GA. Evidence-based psychosocial treatments for attention-deficit/hyperactivity disorder. J Clin Child Adolesc Psychol. 2008;37(1):184-214.
26. Silva AP, Prado SO, Scardovelli TA, Boschi SR, Campos LC, Frère AF. Measurement of the effect of physical exercise on the concentration of individuals with ADHD. PLoS One. 2015;10(3):e0122119.
27. Newcorn J, Weiss M, Biederman J. Non-stimulant medications. Medscape education. Availabe at: www.medscape.org/viewartcle/531493_3. Assessed July 10, 2013.
28. Blader JC, Schooler NR, Jensen PS, Pliszka SR, Kafantaris V. Adjunctive divalproex versus placebo for

children with ADHD and aggression refractory to stimulant monotherapy. Am J Psychiatr. 2009;166 (12):1392-401.

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