Treatment of adults with attention-deficit/hyperactivity disorder

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Abstract: This review focuses on the treatment of attention deficit hyperactivity disorder (ADHD) in adults. It briefly addresses prevalence, diagnostic and differential diagnostic issues specific to adults. Stimulant medication, non-stimulant medication, and psychosocial treatments are thoroughly reviewed. For each class of medication possible mechanism of action, efficacy and side effects are summarized. Special attention is given to the pharmacological treatment for patients with adult ADHD and various comorbidities. In summary, stimulant medications are most effective and combined medication and psychosocial treatment is the most beneficial treatment option for most adult patients with ADHD.

Keywords: adult ADHD, medication, stimulants, cognitive-behavioral therapy

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common developmental disorders (Spencer et al 2007). It is estimated to affect 5%–10% of the child population (Faraone et al 2003) and from 1%–6% of the adult population (Kessler et al 2005). In a recent large epidemiological study in the United States, 4.4% of the adult population was determined to have clinically significant ADHD symptoms (Kessler et al 2006). ADHD is, therefore, a very prevalent disorder across the developmental spectrum.

Nature of the impairment

ADHD was considered for many years to be a disorder limited to childhood due to diminishing externalizing behaviors. However, as longitudinal studies have demonstrated, the symptoms remain clinically significant for the majority of ADHD patients well into adulthood (Weiss and Hechtman 1993). Recent evidence suggests that almost sixty-six percent of individuals diagnosed as children with ADHD, report at least one ADHD symptom causing clinically significant impairment during adulthood (Weiss et al 2002).

ADHD is characterized by behavioral and cognitive symptoms such as hyperactivity, inattention, disorganization, and impulsivity. The symptoms must be severe and cause clinically significant impairment persistently in multiple domains of an individual's life in order to warrant a diagnosis. In childhood, the most problematic symptoms are hyperactivity, impulsivity, and inattention. These problems result in disruptive behavior at home and at school, which frequently initiates clinical referral for diagnosis and treatment. In adulthood the hyperactivity decreases but inattention, disorganization, and impulsivity result in difficulty functioning both at home and at work. The predominant complaints seen in adult patients are trouble organizing and completing necessary tasks related to either higher education or employment. Adult patients with ADHD have higher rates of academic failures and transfers, lower incomes, higher rates of job loss and turnover, high rates of car accidents, and increased

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rates of divorce (Spencer et al 2007). It is also reported that adults with ADHD have a higher prevalence of anxiety, depression (Kessler et al 2006), drug abuse, and antisocial behaviors (Barkley et al 2004) than the general population.

Diagnosis

Diagnosing of ADHD for the first time in adulthood is complex. A childhood diagnosis or childhood symptoms compatible with an ADHD diagnosis are required for an adult diagnosis. However, such a history may not be present in very bright individuals, and/or people who had primarily inattentive subtypes of ADHD, because in these individuals impairment may only become significant when structure and supports decrease and demands increase.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) Text Revision (DSM–IV TR) (American Psychological Association 2000) diagnostic criterion, the symptoms must have started prior to age 7, be age inappropriate, cause impairment in multiple domains and not be caused by other conditions. The DSM-IV TR ADHD diagnosis is broken down into three subgroups: ADHD predominately inattentive; ADHD predominately hyperactive-impulsive; and ADHD combined type. In order for an adult to receive a diagnosis, the adult must have 6 of the 9 listed DSM-IV symptoms in at least one subtype and these symptoms must have caused consistent clinically significant impairment for 6 months or more (American Psychiatric Association 2000).

There are four important limitations in using the DSM-IV to diagnose adults with ADHD. The first is that criteria were determined in field trials of children, and as is typical the criterions were set at the 93rd percentile suggesting the top 7% would receive the diagnosis. However when the same cut offs are used in adults with ADHD the cut offs fall around the 99th percentile. Therefore, the cut offs may not be appropriate for this population and in fact some physicians advocate that 5 of the 9 symptoms are a sufficient number of symptoms for adult patients (Barkley 1990). The second limitation is that the listed hyperactive symptoms are not developmentally appropriate for adults. The third limitation is that childhood symptoms are sometimes difficult for adult patients to recall and there may not be a parent or older sibling who can validate the syndrome starting prior to age 7. When diagnosing adult ADHD, it may be appropriate to change the required age onset to 12. The fourth problem with the DSM-IV TR is measuring clinically significant impairment is difficult for both children and adults, but more so for adults who have complex and different life demands.

Scales, measures, and semi-structured clinical interviews can be efficient means of garnering information to help establish an adult ADHD diagnosis. Scales should not be used exclusively to establish a diagnosis because many psychiatric disorders have features of ADHD. Additionally, most adults experience some of the symptoms of ADHD, such as forgetfulness or disorganization, from time to time, but these symptoms are not consistent with an ADHD diagnosis in most individuals. A trained clinician with the intricate understanding of clinical impairments and the nature of ADHD can use scales and interviews to guide diagnosis.

Differential diagnosis

Psychiatric disorders

Many psychiatric disorders exist that can mimic the symptoms of ADHD in both child and adult populations. The psychiatric disorders that mimic ADHD symptoms include anxiety disorders, mood disorders, adjustment disorders, learning and language deficits, and some psychotic disorders. In addition, it is important to note that individuals dealing with high levels of stress may exhibit the symptoms of ADHD. The presence and severity of possible alternative explanations for patients' symptoms need to be evaluated carefully in order to ensure that the diagnosis is accurate and treatment options can be weighted appropriately.

Medical disorders

A thorough medical history can be useful to help guide diagnosis since many medical conditions can present with symptoms similar to ADHD. Patients with histories of any one of the following should be more carefully evaluated and referred for other evaluations and possibly other treatments as is necessary: developmental disorders, seizure disorders (petit mal), sleep apnea, hearing and vision problems, thyroid disorders, lead poisoning, and hypoglycemia. Additionally, patients currently taking any medications or with histories of severe drug or alcohol abuse need to be evaluated and treated carefully, since the consumption of some medications and drugs can cause ADHD-like symptoms.

While there are specific symptoms that can help to guide differential diagnosis, this matter is not entirely straight forward since individuals with ADHD are often comorbid with other illnesses. Thus, if a patient is suffering with severe symptoms of other disorders, such as anxiety or depression, we first attempt to address the most severely impairing disorder to determine whether the ADHD symptoms improve. If a patient displays moderate symptoms of other psychiatric disorders, it is often a matter of clinical judgment as to how to proceed.

It is very common that adults with ADHD have comorbidities. In a recent large-scale family study 81% of adults with ADHD had at least one comorbid diagnosis, while 56% had at least two comorbid diagnoses (McGough et al 2005). The most common disorders encountered with adult ADHD patients are: substance abuse and d15ependence, mood disorders, anxiety disorders, and personality disorders such as antisocial personality disorder and borderline personality disorder. Multiple studies have demonstrated that up to 50% of adult patients with ADHD have had comorbid substance use problem (Sobanski 2006). Retrospective studies of adults with ADHD have demonstrated that 30%–50% have had one or more episodes of depression, while 40%–60% have had an anxiety disorder throughout their lifespan (Sobanski 2006). Personality disorders and specifically antisocial personality disorder, are seen at increased rates in adults with ADHD (Mannuzza et al 1998). In instances of comorbidity, treatment can be more complex.

Treatment

Treatment of adults with ADHD consists of medication and psychosocial treatment. Each treatment modality addresses particular problems of ADHD patients. The treatments can be administered separately or as is most common, both types of treatments can be combined.

Pharmacological treatment for adult ADHD

ADHD medications are roughly divided into stimulants and non-stimulant medication. Long-acting stimulant preparations are recommended as they result in better patient compliance and longer-lasting, smoother improvement of symptoms.

Stimulant medication

Stimulants include methylphenidate and amphetamine compounds. Stimulants are the most effective medications for the treatment of ADHD, with responsiveness rates in the 70%–80% range (Spencer et al 2005).

Mechanism of action

Our understanding of the mechanism of action of stimulant medications is undergoing constant revision. Although the exact mechanism of action is unknown, these agents are thought to block reuptake of norepinephrine and dopamine into the presynaptic neuron, thereby increasing extraneuronal catecholamines (Fone and Nutt 2005; Arnsten 2006). Norepinephrine is predominantly connected with frontocortical activity, whereas dopaminergic activity is associated with the lower striatal structures. Both stimulants bind the dopamine transporter protein outside of the cell membrane and block dopamine reuptake presynaptically, thus increasing synaptic dopamine (Wilens 2006). It has been demonstrated that striatal dopamine transporter availability in adult patients with ADHD is markedly reduced by methylphenidate, even at a low dose (Krause et al 2000). Besides dopamine reupatke inhibition amphetamine also increases the release of dopamine from presynaptic cytoplasmic storage vesicles and blocks the uptake of dopamine into neuronal cytoplasmic vesicles, making dopamine more available in the presynaptic neuron (Connor 2005). Methylphenidate in low doses, also enhances hippocampal norepinephrine efflux but does not seem to affect dopamine in the nucleus accumbens. The data are consistent with the hypothesis that enhanced noradrenergic neurotransmission, particularly in the prefrontal cortex, contributes to the effects of methylphenidate (Fone and Nutt 2005).

Clinical effects of stimulants

Stimulants have shown a high behavioral efficacy in numerous randomized controlled trials conducted since the 1960s, with improvement noted for 65%–75% of patients in all age groups (Pliszka 2006). Stimulants effectively alleviate the symptoms of ADHD, including poor attention span, distractibility, impulsive behavior, hyperactivity, and restlessness. Stimulants also improve vigilance, cognition, reaction time, response inhibition, and short-term memory (Connor 2005; Hechtman 2005). Methylphenidate in clinical doses improves spatial working memory, set-shifting, and other prefrontal cortex cognitive functions in healthy individuals and in children with ADHD (Arnsten and Dadly 2005). Stimulant medications are also associated with fewer errors on a driving simulator in teens and adults with ADHD. Barkley and colleagues demonstrated that methylphenidate may have a beneficial effect on some aspects of driving, for example less steering variability, slower driving speed, greater use of turn signals, and a fewer impulsive responses (Barkley et al 2005).

Side effects

Side effects of stimulants are dose-dependent, are generally mild to moderate in most patients, and can be managed either by decreasing the dose or changing the time when medication is given (Weiss and Hechtman 1993). Common adverse effects of stimulants include insomnia, anorexia, nausea, decreased appetite, weight loss, headache, increased

blood pressure, elevated pulse, abdominal pain, irritability, and mood lability. Stimulants may also cause tics, which is a frequent reason for discontinuing the stimulant medication in children. In rare cases stimulants may cause seizures, hypertension, psychosis, hepatotoxicity, and in children stimulant may effect growth (Power 2000; Greenhill 2001). Many side effects emerge early in the course of therapy with stimulants and decline in intensity over time. Side effects, such as irritability, developing late in the day may present rebound phenomena and in this case giving a small supplemental dose of stimulant in the afternoon may be helpful.

Initial insomnia is a relatively common side effect of stimulants. However, it is important to make sure to differentiate whether insomnia is a side effect of stimulants or predates treatment. Insomnia as a side effect can be minimized by avoiding doses in the afternoon and evening and by establishing good sleep routines and schedules. In the treatment with short-acting methylphenidate or amphetamine, insomnia may be secondary to a behavioral rebound that occurs with the wearing off of the stimulant's effects on ADHD symptoms (Powers 2000).

Treatment with all stimulants is associated with a mild increase in blood pressure and pulse. Generally, this slight increase is not clinically significant. However, for adults with borderline hypertension and those with antecedent cardiac disease, it could be clinically significant. What to do with patients with borderline hypertension has remained a clinical dilemma. Results of a recent open-label study in adults with ADHD who had a history of treated hypertension or manifest hypertension demonstrated that treatment with mixed amphetamine salt XR did not produce a clinically significant increase of blood pressure and hypertension during the treatment (Wilens et al 2006).

Mood lability may be a result of ADHD rebound symptom or adverse effect of stimulants. If it is a side effect of stimulants, switching to another stimulant (such as methylphenidate or amphetamine) or switching to non-stimulant medication may be warranted. Sometimes, combination therapy with antidepressants may be useful (Weiss et al 1999).

Very rare adverse events can include psychotic symptoms, manic symptoms, aggression, and suicidality. Rarely reports of psychotic symptoms demonstrated visual and tactile hallucinations of insects (Pliszka 2007).

Contraindications for stimulant treatment are: florid psychosis, bipolar I disorder, Tourette's disorder, severe anorexia, and some medical condition such as hypertension, tachycardia, and arrhytmias (Greenhill 2001).

Methylphenidate

Methylphenidate (MPH) is a stimulant that has been clinically available for 50 years, and its efficacy and safety have been thoroughly studied. It is administered orally with a starting dose of 10 mg for adults. The recommended dose is 0.3–1.5 mg/kg/day (Fawcet 2005) and maximum dose for adults ranges from 80 to 108 mg a day. The higher doses of MPH lead to better therapeutic response (Faraone et al 2004).

MPH is rapidly and extensively absorbed after oral administration. After absorption, it undergoes extensive first-pass hepatic metabolism, predominantly by hydrolysis. Eighty percent of the drug is excreted as ritalinic acid, and the remainder is oxidized by a hepatic mixed-function oxidase (Connor 2005).

There are three pharmaceutical formulations of methylphenidate – (1) immediate release or short-acting formulation (brand name Ritalin), (2) sustained release or intermediate-acting methylphenidate (brand name Ritalin SR), and (3) extended release or long-acting methylphenidate (brand names Concerta, Biphentin, Ritalin LA). The release mechanism of the intermediate-acting methylphenidate (Ritalin SR) produces variable results making this preparation less useful.

The main advantage of short-acting MPH products is their usefulness in situations where a supplement to the once daily medication is required or if the patient desires more flexibility over the dosing schedule (CADDRA 2006). The titration schedule is presented later in the paper.

The rates of MPH abuse are minimal compared to those of cocaine and D-amphetamine (Kollins et al 2001). Methylphenidate is most commonly administered orally, which limits its abuse liability compared to the injected or insufflated forms of other stimulants. However, it can be dissolved and injected and, therefore, there is some concern about abuse and diversion of short-acting methylphenidate (Kollins et al 2001).

Clinical trials on short-acting and long-acting MPH formulations are stated in Table 1. Results of these studies have demonstrated that all MPH formulations are safe and effective in the tretment of ADHD symptoms in adults.

Controlled released methylphenidate (Biphentin) has a unique multi-layer release delivery system with a duration of action of 10–12 hours. The capsule is composed of beads. Each bead has two layers where the outside coat provides immediate release of methylphenidate (40% of the total dose) and then the controlled release layer provides 60% of the total dose.

Table 1 Clinical trials on stimulant medication in adults with ADHD

Stimulants' study	N	Method	Outcome	Conclusion
Short-acting stimulants				
MPH* (Spencer et al 1995)	23	Duble-blind crossover study	ADHD symptoms ↓ (78%)	MPH is significantly more effective than placebo
MPH (Spencer et al 2005)	146	Duble-blind randomized study	ADHD symptoms ↓ (76%) No serious CV adverse events	MPH is significantly more effective than placebo Good tolerability
Long-acting stimulants				
Controlled release MPH /Biphentin/ (Jain et al 2007)	39	Double-blind placebo-controlled crossover study	ADHD symptoms ↓ Weight loss	Successful in symptoms control Well tolerated
OROS-MPH /Concerta/ (Fallu et al 2006)	32	Uncontrolled, open label study	ADHD symptoms ↓ Functional improvements (Sheehan scale)	Successful control of symptoms Less functional disability
OROS-MPH /Concerta/ (Biederman et al 2006)	141	Double-blind, randomized, placebo controlled study	ADHD symptoms ↓ ↑Systolic and diastolic blood pressure and heart rate	Successful control of symptoms Concerns about CV tolerability
OROS-MPH /Concerta/ (Reimherr et al 2007)	47	Double-blind, placebo-controlled, crossover study	ADHD symptoms ↓ (41%–42% symptoms reduction)	Less remarkable improvement than in other comparable studies
Mixed amphetamine salts XR /Adderall XR/ (Biederman et al 2005)	223	Double-blind, placebo-controlled study	ADHD symptoms ↓ (sustained improvement up to 24 months) Good tolerance	Sustained symptomatic impovement Well tolerated

*MPH – methylphenidate

The initial dose is 10 mg (CADDRA 2006). Controlled released MPH is available in seven different dosages, and the capsule can be opened so that the drug may be sprinkled on food. It is approved for the treatment of ADHD in children, adolescents, and adults. Results of a randomized, multicenter, double-blind, placebo-controlled, crossover study in 39 adults with ADHD demonstrated significant behavioral improvement in those who received controlled released MPH compared with those who received the placebo. The treatment was well tolerated, and there were no serious adverse events (Jain et al 2007).

OROS methylphenidate (Concerta) is an extended release MPH, that uses an oral osmotic release system (OROS). Clinical trials have shown OROS MPH to have continued action throughout a 10–12-hour period. The capsule has two drug compartments and a water absorption compartment. Water is absorbed and pushes the medication out through a lazer hole at the end of the capsule. Twenty-two percent of the drug is coated on the outside of the capsule and is immediately available. The MPH that is released from the first medication compartment is supposed to provide sufficient improvement of symptoms in the morning. If it is not sufficient, a small dose of short-acting MPH may also be added in the morning (CADDRA 2006). The medication is not officially approved for adults, but at times it is used for this population because of its long duration and once daily administration. However, it is only available in four dosages (18, 27, 36, and 54 mg) and adults may require up to 108 mg, thus doubling the cost when two tablets are needed.

An important advantage of OROS-MPH is that it is associated with less risk of diversion and abuse than the immediate release preparations. Whereas immediate release MPH

can be crushed and parenterally administered as a common way of abuse, the OROS delivery mechanism does not allow the pills to be crushed and injected or inhaled. Moreover, the gradual enhancement of the concentration of MPH within the OROS formulation leads to a slower onset of the blockade of presynaptic dopamine transporter and, thus, to a less detectable feeling of euphoria (Kollins et al 2001; CADDRA 2005; Biederman et al 2006).

Clinical trials have demonstrated that OROS-MPH is well tolerated and significantly more effective than a placebo in of treating core ADHD symptoms and improving executive functions (Biederman et al 2006; Fallu et al 2006).

The profile of its side effects is similar to those of immediate released MPH. With regard to cardiovascular side effects, only a few patients in this study had systolic blood pressure above 140 mmHg and pulse above 114 bpm (Biederman et al 2006). Adults with borderline hypertension should be carefully monitored in terms of cardiovascular parameters.

Methylphenidate transdermal system is a MPH patch that delivers continuous medication release throughout the day. Clinical trials in children with ADHD have demonstrated that MPH transdermal system is generally well tolerated with mild to moderate side effects (Biederman 2006). This treatment option has been approved by the FDA in the United States and approval is being sought in other countries. There are no clinical trials demonstrating the efficacy of methylphenidate transdermal delivery system in adults with ADHD.

Dextroamphetamine

Dextroamphetamine is a common used stimulants, which has been available and studied for many decades. Currently, there are three different formulations regarding the duration of action: (1) Immediate-release dextroamphetamine (Dexedrine), (2) Sustained-release dextroamphetamine (Dexedrine spansule), and (3) Extended-release mixed amphetamine salts (Adderell XR). Dextroamphetamine immediate-release has a short half-life of 4–6 hours and requires multiple dosages two or three times a day. Therefore, it may be considered a second-line agent for adults with ADHD. It is recommended in situations where supplement to the once daily medication is required or if the patients request more flexibility over the dosing schedule (CADDRA 2006). Starting dose for dextroamphetamine is 5 mg and recommended doses are 0.3–1.5 mg/kg with a maximum of 60 mg a day for adults (Wilens et al 2002). After oral administration dextroamphetamine is quickly adsorbed. About a half of a given dose is eliminated unchanged in the urine, while the other half is broken down into various metabolites, mostly benzoic acid (Powers 2000).

Clinical trials on amphetamine compunds are described in the Table 1. Results of these studies have showed that all preparations are safe and effective in the tretment of ADHD symptoms in adults.

Dextroamphetamine sustained release (Dexedrine spansules) releases the active drug substance in a more gradual fashion than the standard formulation. A spansule is a capsule in which part of dose is released promptly, and remaining of dose is released gradually. Thus, its duration of action is a little bit longer, lasting about 6–8 hours (CADDRA 2006). Therefore, the dextroamphetamine sustained release may be given once daily. However, similar to short-acting formulations, dextroamphetamine sustained release is also considered as a second line agent for treatment of ADHD because their duration of action is shorter than that of long-acting formulations. However, in one child study which compared the efficacy of immediate-release and extended-release amphetamine formulations, dextroamphetamine sustained release were significantly more effective at controlling ADHD symptoms than short-acting formulations during the afternoon and in the early evening (James et al 2001).

Unfortunately, there are a few studies which evaluate the efficacy of dextroamphetamine sustained release in adults with ADHD.

Mixed amphetamine salts extended release (Adderall XR)

This formulation includes neutral salts consisting of 75% dextroamphetamine and 25% levoamphetamine, and it comes in a capsule with long and short-acting beads (James et al 2001). An important advantage of extended released mixed amphetamine salts is its extended duration of action. This stimulant formulation covers patients for a period from 10–12 hours. Mixed amphetamine salts XR is available in 6 dosages (5, 10, 15, 20, 25 and 30 mg). Fifty percent of the dose is immediately available resulting in significant improvement in symptoms in the morning without need for augmentation (CADDRA 2006).

Mixed amphetamine salts XR has a good cardiovascular tolerability and may be administered in patients with a mild hypertension who are on stable antihypertensive medication (Wilens et al 2006).

The most common side effects are insomnia, decreased appetite and weight loss, headache, dry mouth, and nervousness (Biederman et al 2005).

Clinical use of stimulants

Choice of medication

Clinical efficacy of methylphenidate and dextroamphetamine is similar with minor variation between these two drugs. Most patients will respond to both drugs. However, 36% of patients respond preferentially to amphetamine compounds while 26% of patients respond preferentially to methylphenidate compounds. Some 10% do not respond to either one (Greenhill et al 1996). Dextroamphetamine has a little longer duration of action (4–5 hours) than methylphenidate (3–4 hours) after oral administration of short-acting formulations of these drugs. The adverse events of both drugs are also similar. However, despite their similar levels of efficacy, some patients have a better response to methylphenidate, while other patients respond better to dextroamphetamine. Therefore, stimulant selection needs to be very individualized.

Nowadays long-acting stimulants are the standards of care. Research about medication satisfaction showed that between 40% and 50% of participants reported that they were satisfied with their short-acting medication, while 70% of patients reported satisfaction with their long-acting medication (Weiss et al 2006). Long-acting stimulant medication has advantage over short-acting medication, because patients with ADHD are likely to forget to take medications three or four times a day. Also they are not usually aware of the functional impairment they experience when the effect of the short-acting stimulants decreases as a result of missing doses. Even in patients who are relatively compliant the burden of taking a medication three or four times a day becomes unsustainable over time. Therefore, long-acting stimulants are the first-line treatment for adult ADHD patients.

Titration of doses

If short-acting methylphenidate or dextroamphetamine is used, the starting dose is 10 mg for methylphenidate or 5 mg for dextroamphetamine (see Table 2). This dose should be titrated upward for 10 mg or 5 mg every 7 days until the optimal benefit or until side effects prevent increases. If no benefits are noted, switching to the other stimulant is indicated.

If long-acting stimulant preparations are used, starting dose for extend released MPH (Concerta) is 18 mg, for the controlled released MPH (Biphentin) is 10 mg, and 5 mg for mixed amphetamine salts XR (Adderall XR). Titration schedule is similar for all formulations and every 7 days they can be increased up to their maximum doses, which are outlined in the Table 2 (CADDRA 2006).

Stimulants show great inter-individual variability in terms of response to particular dose. Accordingly, it is very important not to titrate too quickly patients who are sensitive (slow metabolizers) or keep those who require higher doses on insufficient doses (rapid metabolizers). In treatment of adult patients with ADHD recommended doses may not be adequate. Therefore, thorough titration with accurate registration of response to drug as well as side effects is very important.

Clinical monitoring during stimulant treatment

Once an effective and well-tolerated dose of stimulant medications is achieved, routine clinical monitoring is needed. Regular clinical monitoring with monthly appointments in the beginning of treatment and after that clinical monitoring at least every three months has a great importance in terms of dose adjustments based on residual symptoms and tolerability. During these visits, ADHD symptoms, comorbid conditions, side effects of medication, heart rate, blood pressure, and weight should be monitored, as well as patient's compliance. The findings of the MTA study strongly suggest that active and intensive monitoring of medication improves treatment outcome (MTA Cooperative Group 1999). Many patients are prone to stop taking medication when they do not have regular follow-up appointment.

It is recommended that a reassessment with a trial off medication occurs once a year to assess the need for medication and appropriateness of the dose (Weiss et al 1999). Planned drug holidays may also be helpful in preventing tolerance to the medication.

Nonstimulant medication

Stimulant medications control ADHD symptoms well in most patients with ADHD. However, 10%–30% of patients do not respond adequately to stimulant treatment or have intolerable side effects (Spencer et al 2004). In such cases nonstimulant medications are the next best treatment option for patients with ADHD. Nonstimulant options for adults with ADHD primarily include atomoxetine and at times bupropion and tricyclic antidepressants. Nonstimulant medications are generally less effective in treating ADHD than stimulants.

Atomoxetine

Atomoxetine is a non-stimulant drug that has shown efficacy in ADHD patients. Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter (Wilens 2006), and it

Table 2 Most common medication treatment options for adult ADHD

First line agents	Duration of action	Start dose	Titration schedule	Maximum dose
OROS Methylphenidate HCL (Concerta)	12 h	18 mg qam[a]	↑18 mg every 7 days	108 mg/day
Long-acting MPH (Ritalin LA)	8–12	10 mg qam	↑10 mg every 7 days	80 mg/day
Controlled release Methylphenidate (Biphentin)	10–12 h	10 mg qam	↑10 mg every 7 days	80 mg/day
Mixed Amphetamine salts XR (Adderall XR[c])	12 h	5 mg qam	↑ 5 mg every 7 days	60 mg/day
Atomoxetine (Strattera)	24 h	0.5 mg/kg/day	↑ 0.8 mg/kg/day for 10 days, then 1.2 mg/kg/day	100 mg/day
Second line agents				
Methylphenidate HCL (Ritalin)	3–5 h	10 mg qam and qnoon[b]	↑10 mg every 7 days	100 mg/day
Dextroamphetamine (Dexedrine)	4–5 h	5 mg qam and qnoon	↑ 5 mg every 7 days	60 mg/day
Dextroamphetamine Spansule (Dexedrine spansule)	6–8 h	10 mg qam	↑ 5 mg every 7 days	60 mg/day

Source: (CADDRA 2006; Paykina and Greenhill 2007).
[a]qam – every morning.
[b]qnoon – at noon.
[c]Adderall XR – Adderall extended release.

is approved by the FDA for treatment of ADHD in children and adults in the United States.

The onset of action is slower than with stimulants and the maximum treatment effect may not be reached for several weeks. Atomoxetine is indicated for patients for whom stimulants are contraindicated, for patients with substance use disorders, for patients with tic disorders, or for those who experience severe side effects with stimulant medications.

Atomoxetine does not have an abuse potential, which is an important advantage for those adults with ADHD who are at risk for substance abuse (Weiss and Weiss 2004; Hechtman 2005; CADDRA 2006). Other advantages of atomoxetine are its once daily dosage, less rebound, and a mild anti-anxiety effect, which may be helpful for management of comorbidity (Weiss&Weiss 2004). Starting dose for atomoxetine is 0.5 mg/kg/day . Dose should be increasing after 14 days to 0.8 mg/kg/day and then after another 14 days to 1.2 mg/kg/day. Maximum dose is less than 100 mg/day (CADDRA 2006).

Since atomoxetine is predominantly metabolized by CYP2D6 isoenzyme, caution is indicated for patients who are poor metabolizers of CYP2D6 substrates (eg, 7%–10% of the population). The slow titration will detect these slow metabolizers who will show significant effects at very low dosages (Hechtman 2005). Patients who take medications, which inhibit CYP 2D6, such as paroxetine and fluoxetine may also show significant effects on small dosages (Belle et al 2002; Hechtman 2005). This issue may be important for patients with ADHD who have comorbid depression and take SSRIs.

The most common side effects of atomoxetine are nausea, decreased appetite (in 15%–20% of patients), insomnia, slightly increased diastolic blood pressure and heart rate, decreased libido, sweating, and dysuria (Weiss and Weiss 2004). There is no evidence of other cardiovascular irregularities in atomoxetine treated patients (CADDRA 2006).

The largest studies on evaluation of the efficacy and safety of atomoxetine were two identical randomized, double blind, placebo-controlled multisite studies, which included 536 adults with ADHD. Results of these studies demonstrated that atomoxetine was superior to placebo in reducing ADHD symptoms. Significant improvement was noted in both studies by the second week, and there were no serious safety concerns during the treatment. Significant side effects were dry mouth, insomnia, decreased appetite, erectile dysfunction, sweating, constipation, and nausea (Michelson et al 2003; Spencer et al 2006).

Bupropion

Bupropion is an antidepressant that may be effective in children and adults with ADHD. Precise mechanism of action of bupropion is still unclear. Preclinical data and clinical research indicate that bupropion is an inhibitor of dopamine and norepinephrine reuptake (Fava et al 2005; Wilens 2006). Bupropion is metabolized mainly by CYP 2B6, and thus may cause clinically important interaction for patients treated with SSRIs, especially with fluoxetine. Starting dose is usually 150 mg per day, and maximum daily dosage is 450 mg per day (Fava et al 2005). Canadian guidelines for ADHD recommend lower doses. The starting dose is 100 mg, and maximum dose is 300 mg (CADDRA 2006).

Bupropion is a second-line agent for uncomplicated ADHD and possibly a first-line agent in patients with comorbid substance use disorders and mood disorders. Bupropion is very useful for treating of patients with bipolar disorder because bupropion-treated patients appeared less likely to switch to mania (Wilens et al 2003; Fava et al 2005).

Common side effects are headache, nausea, dry mouth, insomnia, sweating, and constipation. An important possible adverse event is the emergence of seizures. Bupropion is associated with statistically significantly less sexual dysfunction than SSRIs, including orgasmic dysfunction (Fava et al 2005).

Results of multicenter, randomized, double blind, placebo-controlled trial demonstrated that bupropion XL was significantly more effective than placebo and improved ADHD symptoms in adults (Wilens et al 2005). Bupropion is not yet FDA approved for treatment of ADHD.

Tricyclic antidepressants

Tricyclic antidepressants improve mood and decrease hyperactivity, but do not improve concentration and cognitive tasks (Weiss and Hechtman 1993). Desipramine has fewer side effects than other tricyclics and therefore it has been the most studied tricyclic antidepressant in the treatment of ADHD. Desipramine is an active metabolite of tricyclic antidepressant, imipramine. Desipramine selectively inhibits reuptake of norepinephrine at the presynaptic transporter, resulting in increased availability of norepinephrine.

Desipramine has shown efficacy in the treatment of ADHD. Typical daily dose is 1.5–3 mg/kg (Weiss and Hechtman 1993). Therapy should start with a dose of 50 mg and every 7 days this dose can be increased by 50 mg until the optimal benefit are seen. The maximum dose is 300 mg per day (CADDRA 2006).

Research data have shown that desipramine is effective in the treatment of ADHD in adults (Spencer et al 2004), but it is less effective than stimulants. Side effects of desipramine are similar to side effects of other tricyclic antidepressants and include dry mouth, constipation, sweating, blurred vision, insomnia, decreased appetite, tachycardia, increased blood pressure, EKG changes (particularly prolonged QT interval), orthostatic hypotension, and drowsiness. Such adverse effects suggest possible cardiotoxic effects, and this limits the wider use of despiramine in the treatment of patients with ADHD.

Clonidine

Clonidin is α2-adrenergic receptor agonist that has effect on symptoms of hyperactivity and impulsivity, but not those of inattention. Clonidine is considered as a second-line agent in the treatment of ADHD and may be useful in some patients with comorbidity, particularly in the treatment of patients with comorbid ADHD and Tourette's syndrome and other tic disorders (Robertson 2006; Wilens 2006). Common side effects are dry mouth, sedation, drowsiness, dizziness, and constipation (Powers 2000).

Guanfacine

Guanfacine is a direct agonist of the α-2a subtype of norepinephrine receptors, which are particularly numerous in the prefrontal cortex and the locus ceruleus. Guanfacine actions on the α-2a receptors of the locus ceruleus could modulate locus ceruleus discharge rates and result in improved attentional abilities. Attention also could be improved indirectly via locus ceruleus effects on central dopaminergic neuron (Taylor and Russo 2001).

Guanfacine is less sedating and has a longer duration of action than clonidine (Lopez, 2006). Guanfacine is effective treatment for symptoms of ADHD. It is especially helpful for patients with liability for abuse of stimulants. Guanfacine is safe and well tolerated in children and adults with ADHD (Biederman 2006).

Modafinil

Modafinil is an agent that promotes wakefulness and is approved by the FDA for treatment of narcolepsy. Accurate mechanism of its action is not known. Modafinil has several effects on the brain. It is presumed that Modafinil's effects are mediated by activation of noradrenergic α_1 receptors by blocking the reuptake of dopamine in the cerebral cortex and caudate. Modafinil also inhibits γ-aminobutyric acid neurons in the ventrolateral preoptic nucleus, which normally inhibits

noradrenergic neurons in locus ceruleus and histamine neurons in tuberomammillary nucleus. In this way modafinil activates noradrenergic neurons and histamine neurons with resulting "wakeful state". Modafinil increases release of glutamate in the hippocampus and in the thalamus which results in increasing of vigilance. Finally, Modafinil activates hypocretin neurons in the lateral hypothalamus. Hypocretin peptides stimulate the release of histamine; thus again causes arousal (Wilens 2006; Ballon at al 2006).

Modafinil is a well-tolerated drug with mild side effects and with low propensity for abuse. Most common side effects are insomnia, headache and decreased appetite. Modafinil can be administered once daily (Turner 2006). Modafinil film-coated tablets present a new formulation that is administered once daily. Placebo-controlled studies in children and adolescents have shown that this formulation is effective in the full spectrum of ADHD symptoms (Biederman 2006). In order to determine the role of modafinil in the treatment of ADHD, there is a need for large, long-term comparison studies of modafinil and long- and short-acting stimulants (Lindsay et al 2006).

Treatment of ADHD patients with comorbid diagnoses

Approximately 75% of adults with ADHD have at least one comorbid condition. Implications of comorbidity for the treatment are significant because the treatment protocols should involve treatment strategies for both disorders. Some comorbid disorders may adversely influence the response of these adults to medication for ADHD (Barkley and Gordon 2002).

As a general principle the most severe and impairing condition should be treated first with the most effective available medication. Once some improvement is noticed treatment of other condition can proceed using the most effective medication if possible.

ADHD and depression

ADHD and major depressive disorders are among the most common psychiatric disorders occurring in adulthood, and comorbidity rates between them are high.

According to the US National Comorbidity Survey, the prevalence rate of ADHD among adults with major depression is 9.4%, whereas in patients with dysthymia the prevalence rate of ADHD is 22.6% (Kessler et al 2006). Comorbidity between ADHD and major depression is clinically significant, although the clinical presentation of depression is not different among those with ADHD compared to those without ADHD.

Generally, if depression is severe, it needs to be treated prior to treating ADHD. The best strategy for treating ADHD with comorbid depression is a combination of stimulant and antidepressant medications. SSRIs combined with stimulants can be safe and effective, while the chance for potential drug interactions is small (Nutt et al 2006; Prince and Wilens 2000). Combination therapy, which would involve stimulants with serotonergic-noradrenergic reuptake inhibitors (SNRIs), can also be successful, but in such combination it is very important to monitor sympathomimetic side effects, which are present with both classes of drugs. Combining atomoxetine with SSRIs can be difficult since both are metabolized via the cytochrome P450 enzyme system (2D6).

In patients with manic episode or bipolar disorder and ADHD, therapy with mood stabilizers and/or atypical antipsychotics is indicated before the treatment with stimulants. Stimulants carry a potential risk of worsening or triggering bipolar symptoms (Nutt et al 2006) and accordingly bupropion could be a first choice medication for this comorbidity. An open trial of bupropion for the treatment of adult patients with ADHD and comorbid bipolar disorder suggested that sustained-release bupropion may be effective in treating ADHD and it is not associated with significant activation of mania. Most bipolar patients in this research study were diagnosed with bipolar II disorder (Wilens et al 2003; Fava et al 2005).

ADHD and anxiety disorders

Children and adults with ADHD have much higher rates of anxiety disorders than match normal controls (Biederman 2004). Clinical and epidemiological studies demonstrated that lifetime prevalence of anxiety disorders in adult patients with ADHD is 40%–60% (Sobansi 2006). In case of comorbidity of ADHD with anxiety disorders stimulant medications should be the first therapeutic intervention. Anxiety symptoms generally do not worsen on stimulant medication. A second treatment intervention would be specific therapy for anxiety disorders either with SSRIs or cognitive-behavioral therapy (CBT). The most beneficial treatment option is combined therapy.

Initial studies evaluating the response to stimulants in patients with ADHD and anxiety suggested that they had a reduced response to stimulants. However, more recent studies have not supported decreased stimulant response in anxious ADHD patients (Hechtman et al 2005).

In a study of the treatment of adults with ADHD and comorbid anxiety and depressive disorders, Hechtman and colleagues compared the efficacy of paroxetine as

a monotherapy, dextroamphetamine as a monotherapy and the combination of both medications. Results demonstrated that ADHD symptoms markedly improved with dextroamphetamine. Anxiety and depressive symptoms were improved with paroxetine.

Patients who received both dextroamphetamine and paroxetine improved in both ADHD and anxiety/depressive symptoms but not to the same extent as with monotherapy and they had more severe adverse events (Hechtman et al 2003; Weiss et al 2006).

ADHD and substance use disorders

Adults with ADHD and substance use disorders have earlier onset of substance abuse in comparison with adults without ADHD. Nine to 30% of adults with ADHD have problems with drug abuse or dependence (Wilens 2004a).

In the treatment of patients with ADHD and substance use disorders, it is recommended to first treat substance abuse (Nutt et al 2006), although ADHD medication can be initiated along with the treatment for substance use disorder. Atomoxetine, bupropion, tricyclic antidepressants should be contemplated as a first line of treatment for these patients (Wilens 2004b). Active substance abuse is a contraindication for stimulant medications. However, if nonstimulant medications are ineffective, considering a stimulant trial is warranted for patients who are in a stable substance abuse remission. Stimulants are thus considered second-line agents for adolescents and adults with ADHD and substance use disorders (Wilens 2004b). Extended-release or longer-acting stimulants with lower abuse liability and diversion potential are preferable (Wilens 2004a). Treatment with stimulants needs to be performed with special caution and should be carefully monitored.

There has been speculation that a high rate of substance abuse among the adults with ADHD is caused by the use of stimulant medications. Research studies do not support the claim that stimulant treatments add to the risk of substance abuse in the patients with ADHD (Wilens 2004b). Finally, it is important to keep in mind that stimulant treatment generally reduces the risk for substance use disorder.

Psychosocial treatment

Every psychotherapy approach for adult ADHD patients needs to address specific problems they face. These problems are poor time management and organizational skills, impulsivness, insufficient problem solving skills, academic and social failures, problems with self-esteem, difficulties maintaining relationships, temper outbursts, potential antisocial behavior, etc. In order to better clarify all of the problems that may affect adults with ADHD, it is recommended that every psychotherapy treatment contain a psychoeducational component.

Psychoeducation involves teaching patients about their disorder, including how ADHD affects different areas of their lives and relationships, how to recognize symptoms of ADHD, and how to treat it. Psychoeducation is important for treatment compliance and long-term adherence, and it is needed for patients as well as their significant others. Teaching patients about ADHD and its impact on their lives and daily functioning may improve the self-esteem of the patients, who are frequently regarded as lazy or less intelligent.

Psychosocial treatment should be evidence based. Psychotherapeutic modalities, which may fulfill the specific needs of adult ADHD patients, include individual and group cognitive-behavioral therapy, family therapy, and other interventions.

Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) is suitable for adults with ADHD because it is a collaborative model with a good structure. It was designed to promote self-controlled behavior by enhancing self mediation and control strategies (Weiss and Hechtman 1993). Initial trials were based on the conceptualization that impulsive patients with ADHD should be taught to talk to themselves as means of developing self-control.

An important question is what is the mechanism of action of CBT in patients with ADHD. In an attempt to explain the therapeutic effects of different treatments, Rapport and colleagues (Rapport et al 2001) formed the conceptual model of ADHD. According to this model, stimulants have a direct impact on the neurobiological substrate of ADHD, whereas CBT affects the core psychological (ie, behavioral and cognitive) features. Other nonspecific and more supportive psychosocial treatments influence peripheral or secondary features of ADHD, such as job or academic underachievement, inadequate social skills, and disturbed family relationships.

Rostain and colleagues have a different point of view. They hypothesized that patients' symptoms improve in psychotherapy because CBT effectively treats their comorbid conditions rather than the core symptoms of ADHD (Rostain et al 2006).

Cognitive-behavioral therapy for ADHD can be administered in individual or group format. Group format has some advantages. Group therapy provides the opportunities to meet people with similar problems, share information, and learn how others cope with their difficulties (Young 2002).

Literature on the efficacy of CBT in adults with ADHD is sparse. One early retrospective study on the use of CBT in the treatment of adults with ADHD was conducted by Wilens and colleagues (Wilens et al 1999). Patients were treated with an adapted form of Beck's cognitive therapy with a focus on dysfunctional cognitive schemas and cognitive restructuring. Treatment consisted of 36 sessions and, according to a chart review of the symptoms of 26 patients, produced improvements not only in the symptoms of ADHD but also on measures of depression and ratings of overall functioning. There are two important notable limitations of this study. There was no control group and the treatment evaluation was done retrospectively via chart review.

Stevenson and colleagues (Stevenson et al 2002) developed a cognitive remediation program (CRP) for adults with ADHD, oriented to reduce the impact of cognitive impairments. The CRP was designed for a small therapy group and consists of three main components: eight group sessions, once weekly; support people who acted as coaches; and workbooks with exercises. Treatment significantly improved ADHD symptoms, organizational skills, and self-esteem. The limitations of this study are its small sample size (N = 22) and the fact that the assessment of treatment outcomes was done only by self-report ratings.

Rostain and colleagues (Rostain et al 2006) evaluated a combined treatment for 43 adults with ADHD, using concurrent pharmacotherapy and CBT. The CBT consisted of 16 individual psychotherapy sessions over the course of six months. All patients received mixed salts of amphetamine. The results demonstrated that the combination of pharmacotherapy and CBT is effective in the treatment of a wide range of ADHD-related symptoms, symptoms of anxiety and depression, and overall functioning.

Hesslinger and colleagues (2002) evaluated the efficacy of a structured skill-training program in the treatment of adults with ADHD. The therapy was based on the principles of dialectical behavior therapy, modified to suit the specific needs of adults with ADHD. In addition to components of CBT, the treatment included mindfulness. Results of this study showed improvement in ADHD symptoms and an overall reduction of symptomatology, as measured by psychometric scales. However, this study had many limitations, including a very small number of patients (N = 7) and the continuation of medication treatment in some patients (Hesslinger et al 2002).

A model of cognitive-behavioral therapy for adult ADHD that was developed by Safren (2006) involves six modules. Three of them are "core modules" and another three are optional modules. Core modules are organizing and planning, distractibility, and cognitive restructuring. Optional modules are procrastination, anger and frustration management, and communication skills. Safren and colleagues evaluated the efficacy of the cognitive-behavioral therapy for adults with ADHD who have not fully responded to medications alone. Among 31 patients who received CBT 56% were treatment responders compared to only 13% non-responders. Authors concluded that CBT might be a useful component in the treatment for adults with ADHD who do not fully respond to medications alone (Safren et al 2004; Safren 2006). Limitations of this study include no randomization, no control or comparison group, small sample size, and no adequate control of pharmacotherapy.

We developed a cognitive behavioral therapy program for adults with ADHD which included the following twelve modules: psychoeducation (ADHD symptoms, the neurobiology of ADHD and pharmacological treatment), organizational skills training, time management, anger management, stress inoculation training, cognitive reframing, self-control and self-esteem, and relationship management (Galina et al unpublished). Treatment is administered in a group format with once weekly group sessions. Intensive therapy lasts 12-weeks and then patients receive a monthly booster session for three months. Our CBT program includes coaching. Coaches, who are psychologists or student of psychology and medicine who have received special training in coaching activities for cognitive-behavioral therapy. Coaches contact patients by phone twice a week and help them implement CBT strategies outside of the session. This ongoing study will explore the efficacy of CBT in adult ADHD.

Besides the treatment of ADHD, cognitive-behavioral therapy could be very useful for the treatment of comorbid states as well. Cognitive-behavioral therapy may be a particularly effective therapy for adults with ADHD and substance use disorders, especially cognitive therapy interventions and an integrated relapse prevention program (Wilens 2004). For comorbid depression and anxiety disorders, psychosocial interventions particularly a combination of cognitive behavioral therapy and medication, are also very effective.

Family and marital therapy/ counseling

Adults with ADHD have a significantly less successful marital adjustment and family functioning than people

without ADHD. They also have a higher incidence of separation and divorce than normal control. Marital problems are common complaints of adults with ADHD seeking treatment (Eakin et al 2004). Spouses who do not have ADHD usually complain that their partner is unreliable, messy, disorganized, forgetful, a poor listener, etc. Spouses also feel overburdened because they have to take care of all things in the family. Likewise, spouses of ADHD patients think that their spouse does not make a sufficient effort in order to change his/her behavior. Therefore, education about the disorder needs to involve the spouse of ADHD patients as well. Both, the patient and the spouse, benefit from learning about ADHD and its consequences on the patient's behavior and functioning. Gaining a better understanding of ADHD and realizing that many of the patient's behaviors are not a result of a lack of caring or a willful misconduct, may contribute to a reduction of blaming each other (Murphy 2005). Family therapists focus on how patterns of interaction maintain the family or marital problems. Moving the focus from "identified patient" to the interaction between spouses or family members can be useful. Everyone within the family and each spouse has an important role in rebuilding the relationship.

Summary

ADHD is prevalent neurobiological condition, affecting 4.4% of the general population. It is accompanied by high rates of comorbidity (depression, anxiety, substance abuse) and significant social, emotional, and occupational impairments, which affect the patients and their families.

The article briefly reviews prevalence, diagnosis, differential diagnosis, and comorbidity of ADHD in adulthood. However, the major focus of the paper is the treatment of adults with ADHD. The strengths and limitation of medication (stimulant and nonstimulant) treatment as well as psychosocial treatment, particularly cognitive behavioral therapy are summarized.

For each medication or class of medication key aspects such as possible mechanism of action, titration schedule with starting and maximum dosages, therapeutic effects and side effects are outlined. Generally long acting stimulants are the most effective treatment approach. Medication treatment for patients with ADHD and various comorbid conditions, eg, depression, anxiety, bipolar disorder and substance abuse are also described.

Finally, the efficacy of psychosocial treatment, particularly cognitive behavioral therapy is addressed. Combined medication and psychosocial treatment approach are recommended as an effective treatment for most patients with ADHD.

Future research directions

Even though the research literature in ADHD is vast and growing much remains to be done.

1. Etiology and Pathogenesis: The etiology and pathogenesis of ADHD is still in its infancy. Genetic and neurobiology research using modern technology will hopefully clarify these issues in the future.
2. Epidemiology of Adult ADHD: There is one large study conducted in the U.S. by Kessler et al 2006. Epidemiological studies of adults ADHD in other parts of the world are totally lacking.
3. Appropriate Diagnostic Criteria: DSM-IV and ICD-10 diagnostic criteria for adults with ADHD are derived from child studies or clinical presentation of children and are therefore not appropriate for adults. Diagnostic field trials of adults need to be carried out to arrive at appropriate criteria for diagnosing adults with ADHD. Currently its unclear how adults diagnosed as children with ADHD differ from those who are newly diagnosed in adulthood. We know little about the impairment of adults who do not currently meet all diagnostic criteria and have a "subclinical diagnosis".
4. Comorbidity: We need to learn better ways to decrease comorbidity in adults with ADHD and to treat it more effectively when it does occur.
5. Duration of Treatment and Follow up: More research is needed to determine optimal duration of treatment and optimal frequency, type and lenght of follow up. It's clear that short term treatment is effective, but we need to determine how to translate this efficacy into long term positive outcome for patients and their families.

In summary there is still much to be done in the area of ADHD in adulthood.

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