Pharmacotherapy of Adult ADHD and Comorbid Conditions: A Guide for Primary Care Providers

Welcome to Pharmacotherapy of Adult ADHD and Comorbid Conditions: A Guide for Primary Care Providers.

If we’re going to leave you with a single message for today, once you have made a diagnosis of ADHD I want to encourage you to treat the condition. Undertreatment is a significant problem and the impairments from the disorder are quite profound.

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Pharmacotherapy in Adult ADHD

• Stimulants
  – Methylenidate compounds
  – Amphetamine compounds
• Non-stimulants: Atomoxetine
• Pharmacotherapy in Adult ADHD and Co-morbid Conditions

atomoxetine. Additionally, we will be talking about pharmacotherapy of adults with ADHD and comorbid conditions – that is off label. FDA approval is for the medicines noted above for treating ADHD alone. However, ADHD tends to occur commonly with comorbid disorders and, therefore, discussing the treatment of ADHD with another mental health disorder is quite important.

Stimulant Medications Studied for ADHD

This slide depicts the stimulant medications studied for adult ADHD. We should note that there are four FDA approved medications which are all sustained release versions of the psychostimulants. But let’s review the different medications and how they have been studied.

The immediate release methylenidate compounds or other preparations that are not oral sustained release include: Ritalin®, Metadate® which is an intermediate acting methylenidate compound, and Daytrana®, the forms vary with their brand. The duration of action for the immediate release methylenidate is only three to four hours. It is longer for the intermediate acting Metadate® and Daytrana®. Mixed amphetamine salts in the immediate release form (brand name is known as Adderall) is a four salt combination known as mixed amphetamine salts comes in a variety of strengths from 5 mg up to 30 mg. The noted duration of effect is anywhere from four to six hours. We will also present data showing improvement in ADHD symptoms in adults with this preparation; however, it is approved for children but not approved for adults with ADHD.

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Oros methylphenidate is Concerta®, and is a methylphenidate preparation. It involves a pill that has a methylphenidate coating. There are two chambers on the inside part of the pill with a membrane barrier and a laser drilled hole with a reservoir of methylphenidate in the bottom. There is a mechanical sustained release preparation whereby the pressure from the gut fluid slowly pushes the methylphenidate out through the membrane. It comes in a variety of different dosage strengths: 18mg, 27 mg, 36 mg, and 54 mg. The FDA label goes up to 72 mg a day for adults. In fact, the usual starting dose in clinical practice varies from 18 to 30 mg. The duration of action is up to 10 hours and again this is FDA approved for adults with ADHD.

Dexamethasone extended release is Focalin®XR. It is the d-methylphenidate in a sustained release preparation and it is a beaded mechanical sustained release preparation. All methylphenidate compounds, formally as Ritalin®, are d and l preparations and in fact Oros methylphenidate is a combination of a dextro and levo methylphenidate. Here we isolated the d form of methylphenidate and it is in a mechanical sustained release preparation. It comes in a variety of dosage strengths from 5 to 30 mg with the 30 mg strength being a fairly recent addition to the portfolio. The approximate duration of effect is anywhere from 10 to 12 hours. Again, it is FDA approved for adults with ADHD.

Mixed amphetamine salts extended release is Adderall XR®. Again, it is a mechanical sustained release preparation with short and long-acting beads. It has been studied in adult ADHD and is FDA labeled. The dosage strengths vary between 5 mg and 30 mg although the FDA approved label goes to 20 mg, in adults. The approximate duration of effect is again 10 to 12 hours and it is FDA approved.

Lisdexamfetamine dimesylate is Vyvanse®. This is a pro-drug. It has a chemical sustained release which we will talk about. The dosage strengths vary between 20 and 70 mg. Usual starting dose is 30 mg. Titration goes on up to 70 mg. It is FDA labeled up to 70 mg with an approximate duration of effect up to 12 to 13 hours and it is FDA approved for adults with ADHD.

**Studies of Stimulants in Adult ADHD**

Let’s look at some studies of stimulants in adult ADHD. We will actually go through studies that show each of these compounds as mentioned in the prior slide.

**Study of Methylphenidate (MPH) Use in Adult ADHD**

This slide depicts a study done by Tom Spencer using methylphenidate in adult ADHD. It is a comparison between immediate release methylphenidate and a placebo. There are a couple of things to note before we discuss the actual data. The rating scale used here is a DSM-IV ADHD symptom checklist which is quite similar to the ADHD RS. Actually, the symptom threshold you’ll notice is slightly above 20, in part, because the data collected used DSM-III and DSM III-R and extrapolated out to DSM-IV. Classically, the ADHD RS will have the eighteen symptoms in DSM IV rated zero to three on a severity basis. Looking at the data here you’ll see that the methylphenidate given three times a day will drive down ADHD symptoms below the symptomatic threshold for ADHD. These improvements occur starting at week two and continue all the way out with improvement to week six.

**Study of Mixed Amphetamine Salts in Adult ADHD**

These data come from a study of mixed amphetamine salts immediate release in a study of adult ADHD conducted by Tom Spencer. Focus on the first portion of the study, looking again when symptoms are driven below subthreshold for ADHD on an ADHD symptom checklist similar to the ADHD RS. You see the effects of mixed amphetamine salts over placebo starting at week one with significant effects by week two and then driving down below the symptom threshold by week three. So, even though neither immediate release methylphenidate nor immediate release mixed amphetamine salts are approved for adults with ADHD — this would be off label — we do have data that show they are efficacious. Both of these compounds are approved for use in children.

**Study of Mixed Amphetamine Salts Extended Release in Adult ADHD**

This is the registration study looking at mixed amphetamine salts extended release in adults with ADHD. It is a dose ranging, multi-center, double blind study. It is a fairly large study with 248 patients.

The studies we’re going to be showing now have larger samples than the single site studies we showed previously. This study showed that the once daily mixed amphetamine salts was well tolerated and there were significantly lower scores out to twelve hours on the Conners Adult ADHD Rating Scale (CAARS) and the primary outcome showed statistically significant improvement in the ADHD RS. The CAARS is a self-report version which measures similar symptoms to the ADHD RS, but it is slightly different. There was significant improvement in the clinician Global Impression of Severity Rating Scale—CGI scores. Note here, the FDA label on this study is only at 20 mg because the study did not find dose response relationship. Even though subsequent studies have found on severity analysis that patients with more severe ADHD did somewhat better on higher doses, the FDA label on mixed amphetamine salts XR is 20 mg per day.

**ADHD Rating Scale: Mean Total Score at Endpoint (ITT)**

What you see looking at in this four week study, compared to placebo you see an average change on the ADHD RS of a decrease of 6.6 points. Then you see improvements across the range of mixed amphetamine salts from 20 to 40 to 60 mg with improvement mean scores going from decrements of 12.6 to 14.4 points.
coming out of treatment with placebo had a decrease over 10 points on the ADHD RS, and those who had come out of the dexmethylphenidate XR group had an improvement of 8.4%. The drug obviously worked. Similarly they have data from the controlled phase of this study that shows significant effects of dexmethylphenidate XR over placebo. This was a longer study that looked at open label treatment as compared to the double blind study. Dexmethylphenidate XR is FDA approved in ADHD with adults.

Lisdexamfetamine Dimesylate Chemistry

Lisdexamfetamine dimesylate is a prodrug that is therapeutically inactive until it is converted to active d-amphetamine in the body. Lisdexamfetamine consists of dextroamphetamine (d-amphetamine) bonded to an amino acid lyene. It is a chemical sustained release mechanism whereby, once it is absorbed into the bloodstream, it is too large to cross into the brain, the body recognizes it as actually a protein and proteases actually cleave it apart leaving the lycene, which is the amino acid and then the d-amphetamine. This gives you the sustained release mechanism that is fairly long, up to twelve hours. Once the d-amphetamine is in the blood it can obviously cross the blood brain barrier into the brain.

Prescribing Information FDA Approved Stimulants for Adult ADHD

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Form</th>
<th>Recommended Start Dose</th>
<th>Recommended Maximum Dose</th>
<th>Approximate Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oros methylphenidate (DMSO-HPLC)</td>
<td>18 mg, 27 mg, 36 mg, 45 mg</td>
<td>Start with 18 mg or 36 mg each morning</td>
<td>Maximum recommended dose is 72 mg</td>
<td>Up to 10 hours</td>
</tr>
<tr>
<td>dexmethylphenidate extended release</td>
<td>5 mg, 10 mg, 15 mg, 20 mg, 30 mg</td>
<td>Start with 10 mg/day</td>
<td>Maximum recommended dose is 30 mg/day</td>
<td>10 to 12 hours</td>
</tr>
<tr>
<td>mixed amphetamine salts extended release (MAS XR)</td>
<td>5 mg, 10 mg, 15 mg, 20 mg</td>
<td>Start with 20 mg/day</td>
<td>Maximum recommended dose is 30 mg/day</td>
<td>10 to 12 hours</td>
</tr>
<tr>
<td>lisdexamfetamine dimesylate (XLX)</td>
<td>20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg</td>
<td>Start with 50 mg once daily in the morning</td>
<td>Recommended maximum dose is 70 mg once daily in the morning</td>
<td>12 to 15 hours</td>
</tr>
</tbody>
</table>

Prescribing Information FDA Approved Stimulants for Adult ADHD

Here is some prescribing information for the four FDA labeled compounds previously reviewed: Oros methylphenidate, dexamethyl-phenide XR, mixed amphetamine salts XR, and lisdexamfetamine dimesylate. These medications come in a variety of dosage strengths which are noted here.
Starting dose on Oros methylphenidate can be 18 to 36 mg a day, up to 72 mg with an approximate duration up to 10 hours. Dexmethylphenidate XR usual starting dose is about 10 mg, recommended maximal dose in the studies was 20mg and there’s a 30 mg tablet though that is approved. The duration of effect is 10 to 12 hours. Mixed amphetamine salts XR general starting dose noted was 20 mg although most clinicians i think will start at somewhat of a lower dose so probably 10 mg a day. The FDA label in the studies actually list 20 mg, but it is actually higher in kids which is why the package insert will actually note up 30 mg a day and the approximate duration of effect is 10 to 12 hours. Finally, dosages for lisdexamfetamine generally starting at 30 mg once in the morning up to 70 mg with a duration of 12 to 13 hours.

Studies of FDA Approved Non-Stimulant Medication for ADHD in Adults

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Form</th>
<th>Approximate Duration of Action</th>
<th>Approved for Adults with ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>atomoxetine</td>
<td>Strattera®</td>
<td>10 mg, 16 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg</td>
<td>24 hours</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Studies of FDA Approved Non-Stimulant Medication for ADHD in Adults

There is one FDA approved non-stimulant in adult ADHD called atomoxetine hydrochloride or Strattera®. It comes in a variety of dosage strengths varying between 10 and 100 mg a day. The FDA label does go up to 100 mg per day. Duration of effect can be up to 24 hours, but is dosed on a qd or bid basis, and it is approved for adults with ADHD.

Study of Atomoxetine in Adult ADHD

- FDA-approved noradrenergic agent
- Two combined multi-site, randomized, placebo-controlled studies
- Pivotal trials for FDA approval
- N = 280*256 = 536 adults
- Target dosage to 120 mg/d
  - Mean dose circa 92 mg/d
- 10 wk study duration

Efficacy of Atomoxetine in Adults with ADHD

Study results show significant improvement starting by week two with ongoing improvement to week ten based on the CAARS ADHD score. These are the 18 symptoms on the CAARS, which are extracted to match the DSM-IV symptoms and you see improvement going from a little less then 32 down to about 23 over the course of treatment. One thing to note is that atomoxetine’s effect, because it is a reuptake inhibitor, is somewhat slower although it shows significant effects at week two. You do notice this ongoing improvement going out to week ten and because it’s a reuptake inhibitor it does take two to three weeks each time the dose is titrated to get the maximal effect.

Side Effects of Atomoxetine in Adults with ADHD

While there are similarities in the side effects there are some differences between those seen in psychostimulants. We talked about dry mouth and insomnia. The nausea tends to be an early effect and taking the medication with food will diminish this problem. Sometimes ginger can actually help that nausea and that’s a nice clinical pearl. While decreased appetite can be observed, it is sometimes transient and can be improved if it is taken with food. One thing that you see sometimes with atomoxetine that you don’t see as much with psychostimulants is decreased libido or erectile issues. It’s important to talk to your patients about that. A delay in the urinary stream is also something that you can see with atomoxetine which is not seen with psychostimulants. Dizziness can occur. The blood pressure changes were similar to those noted with psychostimulants.

I should note that in the post-marketing surveillance there have been a couple other warnings put on atomoxetine. There is a warning for an allergic type hepatitis that tends to occur one in a million times. There’s no way to screen for it. If patients develop this, they’ll become jaundiced and complain of flu like symptoms. Certainly it is important to discuss that with them. It’s a rare side effect and in the cases that have been observed, stopping medication has been effective in relieving these effects. Additionally, it is important to note that atomoxetine carries a warning on it for suicidal thinking in children, but not in the full adult population.

Prescribing Information FDA Approved Non-Stimulant for Adult ADHD

The prescribing information on atomoxetine is that it’s available in a number of dosage strengths: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, and 100 mg. The recommended starting dose is 40 mg a day on the label. I will say that many clinicians start at a lower dose of either 18 or 25 mg to improve tolerability. Since there is a lag in getting the full onset of, not the initial onset but the full effect of the drug, starting at a higher dose may not actually get you further along and may get you some side effects. I will say in clinical practice, different from the FDA label, many clinicians will start at a somewhat lower dose because it does improve tolerability. Again, dosing is either qd or bid and the recommended maximum daily dose is 100 mg a day and the duration of effect can be up to 24 hours.

Pharmacotherapy of Adult ADHD and Coexisting Psychiatric Disorders

So now we’re going to talk about the pharmacotherapy of adult ADHD with coexisting psychiatric disorders—comorbidities. It’s important to know that this is off label use of ADHD compounds. There really isn’t anywhere near as much of an evidence base here, but let’s review the data we do have available.
Pharmacotherapy of ADHD and Major Depression

- One double-blind study of desipramine
- One placebo controlled trial of paroxetine vs. dextroamphetamine
- One open label trial of venlafaxine +/- stimulants
- One open label trial of sertraline or fluoxetine + psychostimulants

The common comorbidities in adult ADHD include Major Depression, Bipolar Disorder, Dysthymia, Anxiety Disorders, Substance Use Disorders, and Learning Disabilities.

This slide reviews the pharmacotherapy of ADHD and Major Depression. There was a double-blind study done by Tim Wilens investigating desipramine, a tricyclic antidepressant. Margaret Weiss reported on a placebo controlled trial of paroxetine versus dextroamphetamine. There was an open label trial of venlafaxine +/- psychostimulants. Venlafaxine and the addition of the psychostimulants did have improvement in ADHD symptoms. And Rob Findling reported an open label trial of the SSRI sertraline or fluoxetine + psychostimulants. A lot of the data here shows that if you’re going to use an SSRI with a psychostimulant the safety data from the small numbers of studies indicate that they didn’t find a lot of drug interaction and the safety profile looked okay. Remember the evidence base here is fairly small.

One thing to think about when we’re talking about comorbidities is there is no evidence base really to help guide you here but in medicine, when you’re treating more than one condition the general dictum is to treat the most impairing condition first, because that’s going to have the greatest impact on our patients and not treating that condition will have the greatest impairment. It’s important to keep this in mind, if you have a patient with ADHD and Major Depression. Since Major Depression can be life threatening in terms of its suicidality and the ADHD is more lifelong many clinicians will choose to treat the Major Depression first and then treat the ADHD second.

Pharmacotherapy of ADHD and Bipolar Disorder

- One open label trial of bupropion

Wilens T et al. (2006). Arch Gen Psychiatry. 63(12), 1281–1291.

This study, the large scale multi-site NIH supported study actually found that bupropion induced lower switch rates in Bipolar Disorder. Even though it’s an antidepressant bupropion is the most commonly used medication for treating Bipolar Depression. In this study it was effective in treating the ADHD and apparently did not worsen the Bipolar Disorder.

Pharmacotherapy of ADHD and Social Anxiety Disorder

- Controlled trial of atomoxetine — 40–100 mg/day (n=224) vs. placebo (n=218) for 14 weeks
- Significant improvement of ADHD and social anxiety symptoms on atomoxetine

Addl Li et al. (2009). Depression Anxiety. 26(9):270-271

of 218 adults, we actually found significant improvement in the ADHD and also the social anxiety symptoms. The ADHD was rated by our standard measures of the 18 symptoms and the Liebowitz Scale was used for measuring the improvement on social anxiety disorder.

Pharmacotherapy of ADHD and Executive Function Deficits

Executive functioning refers to those neurocognitive processes needed to organize behavior across time and sustain problem-solving toward future goals.

- Effects of Stimulants on Neuropsychological Tests
- Examined neuropsychological test results in group of traditional adults (15–25 years)
- Atomoxetine Treatment of Executive Function Deficit
- Examined effects on executive function during 6 month trial of atomoxetine in Adult Attention Deficit Hyperactivity Disorder (ADHD) patients
- M ild Improvement in all measures of executive functioning

Pharmacotherapy of ADHD and Substance Use Disorders (SUD)

- Atomoxetine (Strattera®) in patients with ADHD and Alcohol Use Disorders
- Atomoxetine in patients with ADHD and Cocaine Abused
- OROS Methylphenidate in patients with ADHD smokers (nicotine)

Pharmacotherapy of ADHD and Executive Function Deficits

Another way that we talk about pharmacotherapy and co-existing condition is Executive Function Deficits. Executive functioning refers to those neurocognitive processes that are needed to organize behavior across time and sustain problem solving for future goals. There are two ways to look at this, one by measuring the effects on neuropsychological tests and another by looking at improvement on clinical measures of executive function deficits. The first study on neuropsychological tests was conducted by Biederman, while the second was done by Tom Brown. Of note is that the Biederman study did find improvement in a number of neuropsychological measures and that the executive function subset on the Brown scale did show improvement with atomoxetine.

Pharmacotherapy of ADHD and Substance Use Disorders (SUD)

Another group of studies looked at pharmacotherapy of ADHD and substance use disorders. A study by Tim Wilens looked at atomoxetine in patients with ADHD and alcohol use disorders. This was a large study that looked at patients that were recently abstinent from significant alcohol abuse or dependence and went into a controlled study of atomoxetine versus placebo. There were significant effects of atomoxetine on the ADHD symptoms in this cohort of patients with very recent abstinence. And of note, subsequent publications investigating safety found that atomoxetine did not cause difficulties with liver function specifically in this group of patients with significant alcohol use disorders. That is a very important thing to keep in mind. Also atomoxetine, a nonstimulant, is not a controlled substance and therefore it is something to think about as a first line therapy for patients with active substance problems.

A subsequent study by Fran Levin in patients with ADHD and cocaine abuse found that Atomoxetine was effective in this cohort. In a recently released e-publication from the clinical trials network looked at Oros methylphenidate in patients with ADHD who were cigarette smokers. Dr. Winhusen found and reported that the Oros methylphenidate substantially improved the ADHD symptoms in adults who had ADHD and smoked. However, it did not increase abstinence rates in terms of smoking. These patients also had a behavioral program and patches to improve treatment for their cigarette abuse.

Summary of Pharmacotherapy for Treating Adult ADHD

- There are five drugs approved by the FDA to treat adult ADHD. Four are long-acting stimulants and one is a long-acting non-stimulant.
- Research has shown these drugs to have long term safety and efficacy in the treatment of adult ADHD.
- Adults with complicated ADHD (ADHD plus comorbid conditions) such as Major Depression, Bipolar Disorder, Anxiety, Executive Function Deficits, and Substance Use Disorder can also be treated with combination therapy.

Summary of Pharmacotherapy for Treating Adult ADHD

To summarize what we know about the pharmacotherapy of treating adult ADHD, there are five FDA approved medications for treating adults with ADHD. Four of these are long-acting stimulants which include Oros® methylphenidate, dexamphetamine XR, mixed amphetamine salts XR, lisdexamfetamine; and, there is one nonstimulant, atomoxetine hydrochloride. Research has shown that these drugs have a good safety profile and are efficacious in the treatment of adult ADHD. The treatment of adults with more complicated ADHD, meaning ADHD with a comorbid condition including Major Depression, Bipolar Disorder, Anxiety Disorder, or Executive Function Deficits, and substance use disorders can be treated with a combination therapy or single use therapy, but the evidence basis here is much smaller than the evidence we have in terms of treating adults with ADHD without comorbidity. And additionally, the use of these ADHD medications in this population with comorbidity is off label. Thank you very much.