## Module 5: Non-Stimulant Treatments for ADHD - Expanding the Therapeutic Toolbox

## Transcript


*Gregory Malzberg, MD. Attending Psychiatrist & Assistant Clinical Professor, Mount Sinai West, New York, NY. Creator, PsychoFarm.*

Dr. Malzberg has no financial relationships with companies related to this material.

[00:00:00] Module 5, non stimulant treatments for ADHD, Expanding the Therapeutic Toolbox. Welcome back. In this module, we'll be discussing the non stimulant treatments available for ADHD in adults. While stimulants are the go to for most patients, there are several reasons why you might consider a non stimulant.

Some patients can't tolerate the side effects of stimulants. Others may have a history of substance use or simply prefer not to take controlled substances. In any case, it's important to understand the options we have beyond stimulants, their unique mechanisms of action, and how to effectively use them in clinical practice.

Non stimulant medications for ADHD. We'll be talking about three main classes of non stimulantsetamoxetine, alpha 2 agonists like guanfacine and clonidine, and a relatively new option called valoxazine. We'll discuss when to consider these medications, how they work, and some of the practical aspects [00:01:00] of prescribing them.

Let's start with adamoxetine, which is Triterra. Adamoxetine was the first non stimulant approved for ADHD and remains a popular choice for patients who either don't respond well to stimulants or prefer a non controlled option. Mechanism of action. Adamoxetine is a selective norepinephrine reuptake inhibitor.

What this means is that it increases the amount of norepinephrine and to a lesser degree dopamine in the prefrontal cortex. This part of the brain is heavily involved in regulating attention, behavior, and executive functioning. By boosting

norepinephrine, adamoxetine helps improve focus and reduce impulsivity in patients with ADHD.

Effectiveness Adamoxetine's effect size is generally smaller than the stimulants. Meta analyses suggest that it reduces core ADHD symptoms. With an effect size of around 0. 4 to 0. 5, compared to 0. 8 or higher for stimulants. [00:02:00] So, it's effective, but may not be as robust as stimulant medications in reducing symptoms.

Dosing. Atomoxetine is typically started at 40 mg daily. After a few days, this is increased to 80 mg. And in some cases, it can go up to a maximum of 100 mg, depending on the patient's response. It's important to note that atomoxetine has a delayed onset of action. It can take 4 6 weeks to see its full benefits, which is quite different from the near immediate effects of stimulants.

Side Effects The most common side effects include nausea, dry mouth, insomnia, and sometimes increased blood pressure. There's also a black box warning for suicidal ideation, especially in younger patients. So, it's important to monitor for mood changes closely, particularly in the first few weeks. To synthesize this all together, adamoxetine stratera is a selective norepinephrine reuptake inhibitor.

Unlike stimulants, it does not affect dopamine in the striatum, significantly reducing the risk [00:03:00] of abuse, making it particularly useful for patients with comorbid substance use disorders. It was actually initially developed as an antidepressant, but it failed in rigorous trials for depression. As an ADHD treatment, adamoxetine has a number needed to treat of about 5 to 7, which is a bit higher than the stimulants, which is a number needed to treat of 2 to 4.

That said, adamoxetine does have distinct advantages. It provides sustained benefit throughout the day, without the rebound effect seen in stimulants. It requires only once daily dosing, and can be prescribed with refills since it's not a controlled substance. A key drawback is its delayed onset. While some symptom relief can be seen within a few weeks, full benefits can take up to 10 weeks to manifest, requiring patients from both clinicians and patients.

While sometimes perceived as better tolerated than stimulants, it does come with its own distinct side effect profile. It doesn't increase energy like stimulants. Instead, it's more associated with somnolence and fatigue, with about 5 [00:04:00] percent of patients experience significant tiredness. It also shares cardiovascular risks with stimulants.

including increased heart rate and blood pressure necessitating periodic monitoring. It's contraindicated in patients with poorly controlled cardiovascular disease, and while it may prolong their QTC interval, routine EKG monitoring is not necessarily required. Other notable concerns include its potential to worsen glaucoma, trigger tics, lower the seizure threshold, and cause hepatic toxicity in rare cases.

Like antidepressants, it carries a warning for increased suicidal ideation in kids and adolescents. Despite some interest in combining adamoxetine with stimulants to enhance ADHD treatment, the safety of this combo remains uncertain. Given the cardiovascular risks, supplementing stimulants with alpha agonists like guanfacine may be a safer alternative.

Guanfacine has also demonstrated modest efficacy in augmenting stimulants while helping to mitigate side effects like [00:05:00] insomnia and hypertension. Atomoxetine's metabolism is heavily dependent on the CYP2D6 enzyme, meaning that its levels can be significantly elevated in poor metabolizers or when combined with strong CYP2D6 inhibitors like fluoxetine, peroxetine, duloxetine, or high dose sertraline.

In these cases, clinicians should start at the lowest dose, titrate more slowly, and aim for a reduced target dose to minimize side effects. For patients with bipolar disorder, adamoxetine should be used with caution. Noradrenergic antidepressants, including adamoxetine, have a higher likelihood of triggering manic episodes.

So when treating ADHD in bipolar disorder or psychotic symptoms, alpha agonists such as guanfacine or clonidine may be a safer alternative. Beyond ADHD, adamoxetine has shown some promise in treating comorbid anxiety and binge eating disorder. A randomized control trial found that it improved both ADHD and [00:06:00] social anxiety symptoms, though the study's industry sponsorship raises concerns about bias.

In summary, atomoxetine remains a valuable, non stimulant option for ADHD, particularly for those with comorbid substance use disorder, those who prefer to avoid controlled substances, or those with comorbid anxiety. However, its slow onset, fatigue related side effects, cardiovascular risks, and potential for drug interactions require careful patient selection and monitoring.

Alpha 2 agonists. Guanfacine and Clonidine. These medications work quite differently from stimulants and adamoxetine. Guanfacine and Clonidine act on alpha 2 adrenergic receptors in the prefrontal cortex, where they strengthen

norepinephrine signaling. This helps improve attention, regulate emotions, and reduce hyperactivity and impulsivity.

Formulations. Guanfacin Extended Release, Intuniv, and Clonidine Extended [00:07:00] Release, Capve, are the extended release formulations typically used for ADHD. While both medications were originally developed for hypertension, they've been found to be effective for ADHD, particularly in patients who struggle with hyperactivity and impulsivity.

Effectiveness The effect size of these medications is fairly solid for a non stimulant, with an effect size of around 0. 6 in improving ADHD symptoms. This makes them a useful option either as monotherapy or as an adjunct to stimulant medications, particularly in patients who experience side effects like irritability or insomnia on stimulants alone.

Dosing, guanfacine extended release. It's typically started at 1mg and can be increased gradually up to a maximum of 7mg daily, though most adults will respond at around 3 4mg. Clonidine extended release. It's dosed a little differently, starting at 0. 1 milligrams with doses titrated up to around 0. 4 [00:08:00] milligrams.

Side effects. These medications can cause sedation, dizziness, and hypotension. In fact, sedation is one of the reasons why guanfacine is often given at night. It can help patients with ADHD who also have sleep difficulties. For clonidine, bradycardia and low blood pressure are more common concerns, so it's important to monitor cardiovascular function regularly.

Alright, let's go into a little bit more detail. Alpha 2 agonists include guanfacine extended release Intuniv and clonidine extended release Capve. They've been FDA approved for pediatric ADHD since 2010, but their use has been limited by lower efficacy compared to stimulants, lack of approval for adults, and historically high costs.

Now that the medications are available in generic form, and new data on adult ADHD have emerged, they're more considered as options for adult ADHD. While guanfacine and clonidine have never been directly compared, Individual trials [00:09:00] suggest similar efficacy. Their onset of action is slower, requiring two to five weeks for full effects, but they offer a unique advantage when used alongside stimulants.

When combined, alpha agonists can mitigate stimulant related side effects. such as anxiety, insomnia, and hypertension, while stimulants reduce the sedation and fatigue commonly seen with alpha agonist monotherapy. However, the additional benefit from alpha 2 agonists as adjuncts is modest, and side effects often limit their tolerability.

In a controlled trial, guanfacine extended release was effective in adult ADHD, but had a 20 percent discontinuation rate due to adverse effects. So, the primary drawback of alpha 2 agonists is their side effect profile. Guanfacine tends to be less sedating than clonidine, but both cause fatigue, dry mouth, constipation, hypotension, bradycardia, and in some cases, QTC prolongation.

Daytime [00:10:00] sedation can be significant, with up to 59 percent of patients experiencing somnolence on guanfacin monotherapy, though this drops to 11 percent when combined with a stimulant. Adjusting dosing to the evening can help mitigate daytime drowsiness. Importantly, sudden discontinuation, especially with clonidine, can lead to rebound hypertension, which makes it essential to gradually taper these medications.

Beyond ADHD, alpha 2 agonists have been explored for various psychiatric uses. Clonidine, in particular, has demonstrated benefits in PTSD related nightmares, Irritability and autism, bipolar mania, and even self harm and borderline personality disorder. Both guanfacine and clonidine can aid in nicotine cessation, alcohol withdrawal, and opioid detoxification by alleviating withdrawal symptoms and reducing cravings.

Overall, alpha 2 agonists are not first line treatments for ADHD, but they serve an important [00:11:00] role in patients for whom stimulants are not tolerated or appropriate. They're particularly useful in individuals with comorbidities such as PTSD, Bipolar, Borderline Personality Disorder, and Substance Use Disorder, where stimulants can exacerbate symptoms.

However, their side effect burden and high dropout rates limit their broad applicability. Careful titration, monitoring of cardiovascular effects, and patient education on delayed onset and possible sedation are key to successful use. Our next medication is bupropion, or Welbutrin. Bupropion is an off label option for treating ADHD, which is especially useful for patients who may have comorbid depression.

It's a non stimulant medication that can be a good alternative when stimulants are not tolerated. Mechanism of action. Bupropion is classified as a norepinephrine

dopamine reuptake inhibitor, NDRI. It works by increasing the levels of norepinephrine and dopamine in the brain, the [00:12:00] two neurotransmitters that play a key role in regulating attention and behavior.

Stimulants typically cause a rapid direct release of dopamine and norepinephrine in the synapses, leading to a faster and more immediate effect on ADHD symptoms. Bupropion, on the other hand, works by gradually inhibiting the reuptake of these neurotransmitters, which results in a slower and more sustained increase.

This leads to a more gradual improvement in symptoms without the immediate burst of effects that the standard stimulants provide. Furthermore, bupropion lacks the more direct stimulant effect on dopamine in regions of the brain associated with reward, making it less likely to be abused compared to traditional stimulant medications.

Effectiveness. While not as robust as stimulant medications, bupropion has shown moderate efficacy in reducing ADHD symptoms. Its effect size is generally lower than that of stimulants, But it can still improve attention and reduce impulsivity, particularly in patients who [00:13:00] cannot tolerate or prefer not to use stimulant medications.

Dosing. Bupropion is typically started at 150mg per day and can be titrated up to 300mg or even 450mg depending on patient's response. The medication comes in three formulations, immediate release, sustained release, and extended release, with the extended release, XL, being the most convenient due to once daily dosing.

Full benefits may take several weeks to manifest, so it requires more time to assess its effectiveness compared to stimulants. Side effects. The most common side effects of bupropion includes insomnia, dry mouth, and jitteriness. It can also increase the risk of seizures, especially at higher doses. Making it contraindicated for patients with a history of seizure disorder or eating disorders like bulimia or anorexia.

Bupropion is less likely to cause weight gain or sexual side effects compared to standard antidepressants. When to consider bupropion? [00:14:00] Bupropion is a good option for patients with co occurring depression, or for those concerned about the potential for stimulant misuse. It's also useful when stimulants cause too many side effects or are not well tolerated.

However, clinicians need to be cautious about using bupropion in patients with a history of seizures or eating disorders due to an increased seizure risk. Now let's

talk about a relatively newer option, valoxazine, sold under the brand name Quelbri. Valoxazine is a norepinephrine reuptake inhibitor that was FDA approved for ADHD treatment in 2021.

Like adamoxetine, shatera, valoxazine primarily increases norepinephrine activity, but it also has some action on serotonin receptors, which may contribute to its unique clinical effects. While stimulant medications remain the most effective treatment for ADHD, valoxazine offers an alternative for patients who cannot tolerate stimulants or are at risk for misuse.

Efficacy and onset of action. Phyloxazine has [00:15:00] demonstrated efficacy in reducing ADHD symptoms in adults, with clinical trials showing improvements similar to adamoxetine, but less robust than stimulants. A key advantage with phyloxazine is it appears to have a faster onset of action than adamoxetine, with some patients reporting symptom relief within one to two weeks.

Whereas adamoxetine often takes 2 4 weeks. However, there are no direct head to head studies comparing valoxazine with other ADHD medications. So, its relative efficacy remains uncertain. Dosing and Practical Use Valoxazine is available in extended release capsules, 100, 150, and 200 mg. The recommended starting dose for adults is 200 mg daily, with weekly titration in 100 mg increments up to 400 600 mg.

depending on response and tolerability. Given its ER formulation, it's typically taken once daily. Side effects and safety concerns. Common side effects include somnolence, fatigue, nausea, and [00:16:00] gastrointestinal discomfort. It also carries a warning for suicidal ideation, similar to atomoxetine, so monitoring mood changes is essential, particularly in patients with comorbid depression or mood instability.

Additionally, valoxazine is a potent inhibitor of CYP1A2, meaning it can interact with medications like duloxetine, tizanidine, and theophylline. When to consider valoxazine? So, it can be a good option for adults with ADHD who don't respond well to adamoxetine and are looking for another non stimulant alternative.

Or they prefer a medication with a slightly faster onset of action than adamoxetine. It also may be beneficial in patients who have comorbid mood disorders, given valoxazine's additional serotonin activity. The bottom line, valoxazine is a newer non stimulant option for ADHD with a mechanism similar to adamoxetine, but with additional serotonin activity.

Its slightly faster onset of action makes it a potential alternative for patients who don't [00:17:00] respond well to adamoxetine. Moving on from the individual medications, what are some clinical considerations for non stimulants? So when do you choose a non stimulant over a stimulant? There are a few key situations.

The first is substance use concern. So patients with a history of substance use disorder may benefit more from non stimulants. As they have a reduced abuse potential. Patients with comorbid anxiety or mood disorders. Stimulants can sometimes exacerbate anxiety or mood instability. So non stimulants are a safer option for patients with significant comorbidities.

Shortera might be especially effective for anxiety, and valoxazine may be especially effective for mood. Partial response to stimulants. In some cases, non stimulants are used adjunctively with stimulants. For instance, a patient might take a stimulant for primary ADHD symptom control, And add guanfacine or clonidine to manage side effects like insomnia or emotional dysregulation.[00:18:00]

Non stimulants tend to have a slower onset than stimulants, so it's important to set the right expectations with patients. It can take 4 6 weeks to see full symptom relief with medications like adamoxetine. Encourage patients to stick with medications during this time to make sure you give it a chance to work.

Monitoring for non stimulants. Non stimulants require a different approach to monitoring compared to stimulants. Here are a few key areas to keep in mind. Blood pressure and heart rate. Both guanfacine and clonidine can lower blood pressure and slow heart rate, so you need to monitor these regularly, particularly during dose titration.

Bupropion, adamoxetine, and valoxazine, on the other hand, increase blood pressure and heart rate, especially at higher doses, so it's important to monitor these parameters. Mood changes. With adamoxetine, valoxazine, and bupropion, it's important to watch for mood changes, especially in the first few weeks of treatment.

Adamoxetine and valoxazine carry warnings for [00:19:00] suicidal ideation, particularly in younger patients and those with pre existing mood disorders. Regularly check in with patients, asking about changes in mood, increased irritability, or feelings of depression. Sedation. For guanfacine and clonidine, sedation is a common side effect.

This can be useful if the patient has trouble sleeping, but if it becomes too much of a burden during the day, consider adjusting the dose timing. Giving the medication all at night instead of in the morning can help. Eupropion, on the other hand, is more likely to cause insomnia rather than sedation, so it's important to monitor for sleep disturbances and consider adjusting dosing time accordingly.

Long term use of non stimulants Non stimulants, especially adamoxetine, can be used effectively over the long term. Studies show that patients who respond well to adamoxetine continue to benefit from it over six months to a year. However, as with any long term treatment, it's important to reassess periodically to make sure the patient is still benefiting and isn't experiencing new [00:20:00] side effects or diminishing returns.

Let's talk a little bit about supplementation for ADHD. So supplements can play a supportive role in managing ADHD symptoms, though they're not a substitute for traditional medications. Some supplements have been studied with varying degrees of scientific support. Here's a quick guide for clinicians on the most promising options.

Omega 3 fatty acids, particularly EPA, has shown some efficacy in helping with ADHD symptoms. Meta analyses suggest a small but significant benefit, especially when used to augment stimulant medication. Doses of about 1 gram of EPA daily have been effective, with improvements often taking up to 3 months to emerge.

The studies that show benefit tend to use formulations with a high EPA to DHA ratio, around 2 to 1. Next is zinc. So zinc deficiency has been linked to ADHD, and supplementation may be helpful, but really only in individuals with low [00:21:00] zinc levels. Studies suggest that around 15 mg per day of zinc gluconate or zinc sulfate can help augment treatment with stimulants.

However, this effect may be more pronounced in countries where zinc deficiency is common, such as Iran or Turkey, compared to places like in the U. S. where the population's deficiency rate is lower. These supplements can serve as adjuncts to medications, but should not be considered first line treatments.

Conclusion In summary, non stimulant medications offer a valuable alternative for treating ADHD in adults. Particularly for those who can't tolerate stimulants or who have other health concerns that make stimulants less appropriate. Atomoxetine, guanine, clonidine and the newer option dioxazine each have their place in the treatment toolbox, and understanding when and how to use them can help ensure better outcomes for your patients.

Non stimulants may not provide the immediate relief that stimulants do. But for many patients, the slower, steadier effect is a good fit, [00:22:00] especially if stimulants have caused issues like anxiety or insomnia. Remember, the key to success with these medications is patience and close monitoring. And regarding supplements, some, like omega 3s, may offer mild benefits for ADHD.

But they should be viewed as complementary treatments, not primary interventions. That wraps up this module on non stimulant treatments for ADHD. In the next session, we'll explore non pharmacological treatments, focusing on behavioral strategies and things you can implement in medication management appointments.

Thank you for listening. I look forward to seeing you in the next module.