Non-Stimulant Medications in ADHD

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- **The most common questions asked by parents and patients focus on:**

✓ whether to start a medication

✓ the effects, side effects or potential safety issues

✓ how long medication will be needed

- Parents or caregivers and patients should be involved in a discussion of realistic expectations and limitations of medication treatment of ADHD as well as how response will be evaluated

Treatment consideration

- Severity of the core symptoms and related impairments
- Comorbid conditions (medical and psychiatric)
- Protective factors, including those related to social context (family, school, peers, and social supports)

Psychoeducation

- To address the persistent myths about ADHD treatment
- Emphasizing that medications primarily target symptoms and do not alter underlying mechanisms or immediately impart social-behavioral skills
- Monitoring of target behaviors and potential adverse effects

- A shared decision-making approach with adolescents is recommended to promote engagement and improve the ability to monitor and manage treatment adherence

Pharmacological Interventions

- Stimulant medications (FDA-approved)
- Nonstimulant medications (FDA-approved)
- Off-label antidepressant medications

FDA-Approved Non stimulant Medications

- Atomoxetine
- Clonidine ER
- Guanfacine ER

Off-Label Medications

- Bupropion
- Tricyclic antidepressants
- Modafinil

Atomoxetine

- ATX was approved by the FDA in 2002 for use in treating ADHD in children and adults
- Its effect size (0.62) appears smaller than that of stimulants (0.94)

Faraone et al. 2003 Hammerness et al. 2009b; Simpson and Plosker 2004

Pharmacokinetic

- ATX is metabolized by CYP2D6
- Variation in this gene can result in an eightfold to tenfold difference in drug exposure between poor and extensive metabolizers

ATX

- Selectively blocks the norepinephrine transporter, a protein that regulates the extracellular concentration of norepinephrine
- Results in the increased availability of norepinephrine in the synaptic cleft
- Increase extracellular dopamine in the prefrontal cortex

Atomoxetine

- Atomoxetine is well-absorbed after oral administration and is minimally affected by food

- Maximal plasma concentrations are reached approximately 1 to 2 hours after dosing

- Some response to ATX can be observed within the first week of administration, further gradual improvement typically occurs over the ensuing 4–6 weeks

Selection of agent

- ATX is considered to be a second-tier agent, after the stimulants
- The CMAP (children's medication algorithm project) recommends a stimulant treatment as the first stage
- Atomoxetine as the first medication for ADHD in individuals with an active substance abuse problem, co morbid anxiety or tics

Atomoxetine

- Available in 10, 18, 25, 40, 60, 80, 100 mg cap
- Starting dose: Children and adolescents <70kg:0.5mg/kg/day for 4 days; then 1 mg/kg/day for 4 days; then 1.2 mg/kg/day
- FDA Max/Day: Lesser of 1.4mg/kg or 100mg
- Off-label Max/Day: Lesser of 1.8 mg/kg or 100 mg

Dosage & Administration

Initial, Target and Maximum Daily Dose

Body Weight	Initial Daily Dose	Target Total Daily Dose	Maximum Total Daily Dose
Children and adolescents up to 70 kg	0.5 mg/kg	1.2 mg/kg	1.4 mg/kg
Children and adolescents over 70 kg and adults	40 mg	80 mg	100 mg

should be administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening.

General Dosing Information

- may be taken with or without food
- can be discontinued without being tapered
- capsules are not intended to be opened, they should be taken whole.

Dosing in Specific Populations

- **Dosing adjustment for hepatically impaired patients**

- For patients with moderate HI, initial and target doses should be reduced to **50%** of the normal dose

- For patients with severe HI ,initial dose and target doses should be reduced to **25%** of normal

Dosing in Specific Populations

- **Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs**
- In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine should be initiated at 0.5 mg/kg/day and **only increased** to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated**.**

Most common adverse reactions

Child & Adolescent

- Nausea
- Vomiting
- Fatigue
- Decreased appetite
- Abdominal pain
- Somnolence
- Headache
- Small but persistent effect on growth (height, weight, and BMI)
- Agitation

Adult

- Constipation
- Dry mouth
- Nausea
- Decreased appetite
- Dizziness
- Erectile dysfunction
- Urinary hesitation

Contraindications

- ✓Hypersensitivity
- ✓Monoamine Oxidase Inhibitors (MAOI)
- ✓Narrow Angle Glaucoma
- ✓Pheochromocytoma
- ✓Severe Cardiovascular Disorders

Warnings & Precautions

Suicidal Ideation – Monitor for suicidality, clinical worsening, and unusual changes in behavior.

Severe Liver Injury – Should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury.

Emergent Cardiovascular Symptoms – Patients should undergo prompt cardiac evaluation.

Effects on Blood Pressure and Heart Rate – Increase in blood pressure and heart rate; orthostasis and syncope may occur.

Bipolar Disorder – Screen patients to avoid possible induction of a mixed/manic episode.

Warnings & Precautions

Aggressive behavior or hostility should be monitored.

Possible allergic reactions, including anaphylactic reactions, angioneurotic edema, urticaria, and rash.

Effects on Urine Outflow – Urinary hesitancy and retention may occur.

Priapism – Prompt medical attention is required in the event of suspected priapism.

Growth – Height and weight should be monitored in pediatric patients.

α2 -Adrenergic Receptor Agonists

- Clonidine is an α2 agonist that binds to—α2A, α2B, and α2C—whereas GUAN binds relatively more selectively to the α2A receptor

- Guanfacine might be better tolerated (i.e., less sedation and hypotension) and more effective cognitively than CLO

- The mechanism of action: a direct noradrenergic agonist at postsynaptic α2 receptors in the PFC

- Outcomes in clonidine, have been measured and observed over several weeks

Guanfacine

- GUAN IR is absorbed more rapidly than the ER formulation (Tmax 2.6 hours [IR] vs. 6.5 hours [ER])

- The overall effect size of the α2 agonists is lower than that of the stimulant medications

Drug Interaction

- Phenytoin and carbamazepine or inhibitors such as fluvoxamine should be used with caution and may require dose adjustments

Clonidine IR (dosage)

- 0.003–0.005 mg/kg/day
- Starting dose 0.05 mg hs
- Given tid-qid
- Increase dose by 0.05 mg/day q week
- Onset within 60 minutes
- Duration 8 hours

Clonidine ER

- 0.1–0.4 mg/day
- Starting dose 0.1 mg qd
- Divide doses > 0.2 mg/day
- Increase dose by 0.1 mg/day q week

Guanfacine IR

- 0.5–2 mg/day for 27–40.5 kg individuals
- 1–3 mg/day for 40.5–45 kg individual
- 1–4 mg/day for > 45 kg individuals
- Starting dose 0.5–1 mg hs
- Given bid-qid
- Increase dose by 0.5 mg/day q week

Guanfacine ER

- 0.05–0.12 mg/kg/day
- Starting dose 1 mg qd
- Increase dose by 1 mg/day q week

Side effects

- Sedation : tolerance does not usually develop
- Fatigue
- Constipation
- Dry mouth and eye
- Hypotension
- Dizziness
- GI discomfort
- ECG changes : decreased HR, increased PR interval, and increase in QTcF
- Rebound hypertention

Uncommon CNS adverse effects of clonidine

- Insomnia
- Anxiety
- Depression
- Rare CNS adverse effects include: vivid dreams, nightmares, and hallucinations
- Fluid retention associated with clonidine treatment can be treated with diuretics

Withdrawal symptoms of clonidine

- Anxiety
- Restlessness
- Perspiration
- Tremor
- Abdominal pain
- Palpitations
- Headache
- A dramatic increase in BP

Withdrawal symptoms

- About 20 hours after the last dose of clonidine, (may also be seen if one or two doses are skipped)
- About 2 to 4 days after discontinuation of guanfacine, but the usual course is a gradual return to baseline BP over 2 to 4 days.
- Doses of clonidine and guanfacine should be tapered slowly.

- Adults should not take clonidine and guanfacine if:

✓ their BP is below 90/60 mm Hg

✓ they have cardiac arrhythmias, especially bradycardia

Noradrenergic Reuptake Inhibitors

- TCA

TCAs

- TCAs were introduced into ADHD treatment in 1974 (Rapoport et al. 1974)

- Clinical trials found efficacy for these drugs when compared with placebo, especially TCAs with more potent noradrenergic activity (e.g., desipramine)

- Associated with significant side effect and safety concerns, including lethality in overdose and increased cardiac risk

Off-Label Medications

- Antidepressants

- ✓ TCAs
- ✓ MAOIs (selegiline, …)
- ✓ Bupropion SR, Bupropion XR (3-6 mg/kg)
- ✓ Venlafaxine XR (1-3 mg/kg)

Bupropion

- an aminoketone originally developed:

✓ as an antidepressant

✓ for smoking cessation

✓ for ADHD

✓ mediated through reuptake inhibition of dopamine and norepinephrine, much like the stimulants

Bupropion

- An elimination half-life of 21 (± 9) hours, and steady state is achieved within 8 days

- The largest proportion of first-pass metabolism is catalyzed by the CYP2D6 isoenzyme

- A multisite double-blind PBO-controlled trial that enrolled 109 patients (bupropion n = 72; PBO n = 37) (Conners et al. 1996)

- Clinically meaningful changes in symptoms and behavior were observed by teachers, but parents did not report the same degree of change

Bupropion

- The dose of bupropion (3 to 6 mg/kg/day) ranged from 50 to 200 mg/day in divided doses

Bupropion

- Maximum dosage is 450 mg/day for the IR and 24-hour ER formulations and 400 mg/day for the 12-hour ER formulation
- The IR formulation is given in divided doses two to three times a day, with a maximum of 150 mg per dose.
- The 12-hour ER formulation is given twice a day
- The 24-hour formulation is given once a day in the morning.
- On the basis of tolerance and response, doses are gradually increased every 2–3 weeks

Bupropion

- The risk of seizure increases almost tenfold at dosages between 450 and 600 mg/day
- At-risk populations include patients with known seizure disorders and those with a current or prior diagnosis of bulimia or anorexia nervosa
- Bupropion is contraindicated in the treatment of these patients

- Other side effects of bupropion include:

✓ Agitation
✓ insomnia
✓ skin rashes
✓ nausea, vomiting
✓ constipation
✓ tremor

The most commonly reported side effects were gastrointestinal (nausea and vomiting) and dermatological (rash)

Modafinil

- A 2-dimethyl sulfinyl acetamide

- Modafinil was originally released in France in 1984 and then approved in the United States in 1998 as a “vigilance-enhancing” agent for the treatment of narcolepsy (Minzenberg and Carter 2008)

Modafinil

- May reduce ADHD symptoms via the same mechanism by which it improves wakefulness: selective activation of the cortex without widespread central nervous system stimulation (Greenhill et al. 2006)

- May potentiate both dopamine and norepinephrine neurotransmission (Minzenberg and Carter 2008)

Modafinil

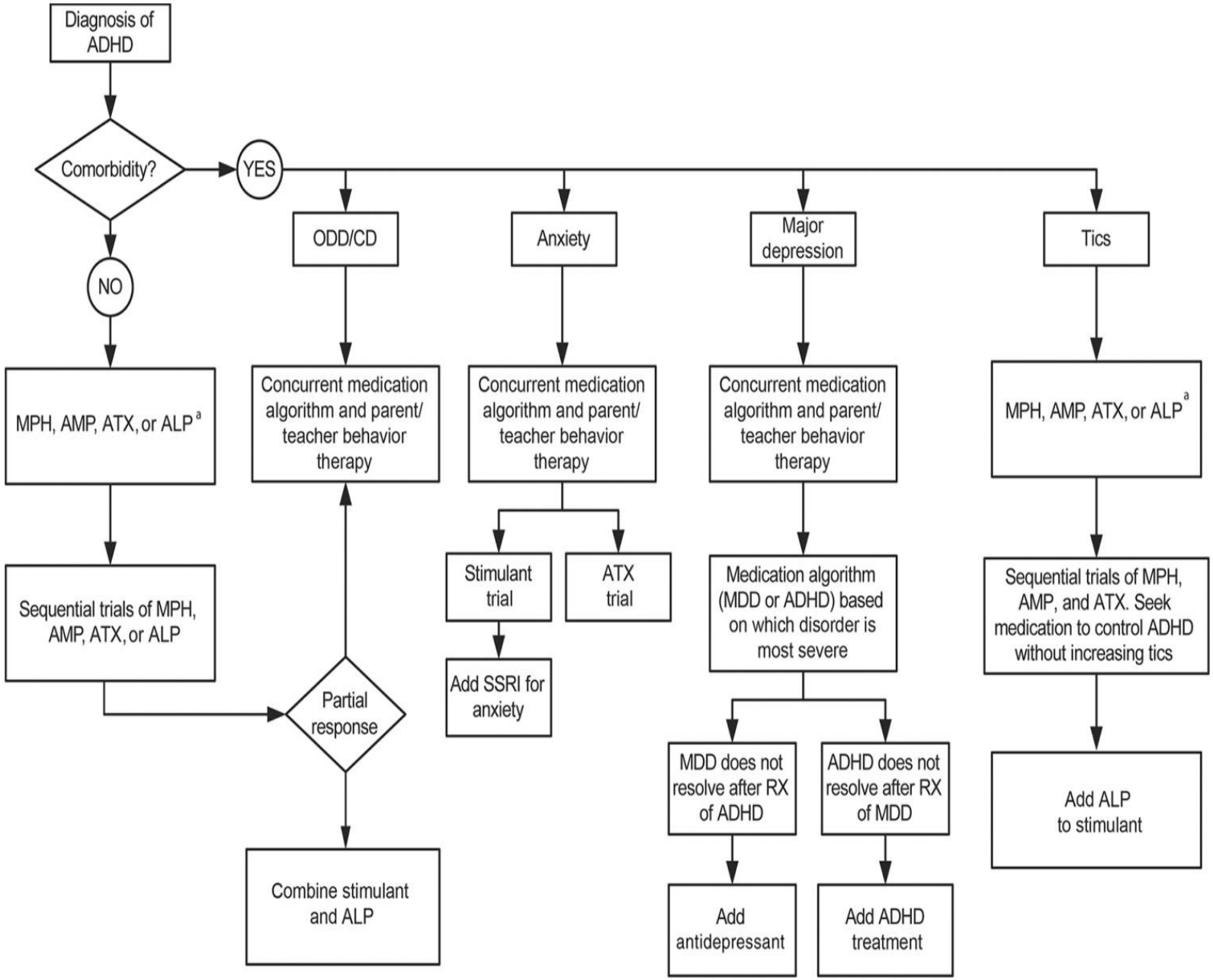
- ✓ It does not activate the areas of reward and abuse in the brain
- ✓ Increased efficacy with higher dosages(340-425mg/day)
- ✓ Significant improvement were observed in a large RCT by Biederman et al(2005)
- ✓ Risk of serious Stevens-Johnson-like rashes

New Agents

- Viloxazine hydrochloride is a norepinephrine reuptake inhibitor with selective serotonin modulation activity

- The Schedule IV stimulant mazindol (a tricyclic compound with central nervous system stimulant properties similar to those of amphetamine) as well as centanafadine, a triple norepinephrine-dopamine-serotonin reuptake blocker (considered to be a stimulant with nonstimulant characteristics)

Konofal et al. 2014; Wigal et al. 2018, Nageye and Cortese 2019.


Diagnosis of ADHD
Comorbidity?
YES
NO
ODD/CD
Anxiety
Major depression
Tics
MPH, AMP, ATX, or ALP[a]
Concurrent medication algorithm and parent/ teacher behavior therapy
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MPH, AMP, ATX, or ALP[a]
Sequential trials of MPH, AMP, ATX, or ALP
Partial response
Stimulant trial
ATX trial
Add SSRI for anxiety
Medication algorithm (MDD or ADHD) based on which disorder is most severe
Sequential trials of MPH, AMP, and ATX. Seek medication to control ADHD without increasing tics
Combine stimulant and ALP
MDD does not resolve after RX of ADHD
ADHD does not resolve after RX of MDD
Add ALP to stimulant
Add antidepressant
Add ADHD treatment

Stimulants with α2 -Adrenergic Receptor Agonists

- 1) achieving desired behavioral outcome
- 2) desired cognitive improvement
- 3) synergy between these compounds
- 4) the sedative effects of the α2 agents may provide an alternative late afternoon or early evening treatment strategy

- There is limited evidence regarding the potential for added benefit

Stimulants and Atomoxetine

- Although these studies suggest a possible role for augmentation of ATX with MPH, the data are very limited, and further study is warranted

Recommendation

- Patients should be assessed periodically to determine whether there is continued need for treatment or if symptoms have remitted.

- Treatment of ADHD should continue as long as symptoms remain present and cause impairment

Thank you for your attention