Comprehensive Pharmacological Treatment Plan in ADHD

Rozita Davari Ashtiani

Child & Adolescent Psychiatrist

Shahid Beheshti University of Medical Sciences

- **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

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)

- 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

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

Pharmacotherapy of ADHD Reduces Risk for SUD: Four year follow-up

- Original cohort re-examined four years later
- Unmedicated ADHD (n=19), Medicated ADHD (n=56), Control (n=137)
- Rates of SUDs were:
  - Unmedicated ADHD: 75%
  - Medicated ADHD: 25%
  - Controls: 20%

Biederman J. (2003). Pharmacotherapy for ADHD decreases the risk for substance abuse: Findings from a longitudinal follow-up of youths with and without ADHD. *J Clin Psychiatry* 64(suppl. 11), 3-8.

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

- The core symptoms of ADHD and associated impairment can persist into adulthood in up to 40% of patients

- It is prudent to periodically reassess the need for ongoing pharmacotherapy

Sibley MH 2017

Comprehensive Treatment Plan in ADHD

- Pharmacological Interventions

- Nonpharmacological Interventions

Pharmacological Interventions

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

FDA-Approved Medications

- Methylphenidate
- Amphetamine
- Methamphetamine (very rarely used)

- Atomoxetine
- Clonidine ER
- Guanfacine ER

Off-Label Medications

- Bupropion
- Tricyclic antidepressants
- Modafinil

Stimulants

- Clinical experience with and research on stimulant use in ADHD started in 1937, and stimulants are among the best-studied pharmacological interventions

Stimulants

- The stimulant response rate is 70%
- The response rate can approach 85% when the two major classes of stimulant medications are tried sequentially

(Connor and Steingard 2004)

Stimulants

These drugs have been shown to enhance dopaminergic and noradrenergic neurotransmission in the central nervous system and peripherally

(Volkow et al. 2001)

Stimulant medications

- Amphetamines
- Methylphenidate

Amphetamines

- Immediate-release: Adderall, Dexedrine, Dextrostat

- Extended release: Adderall XR, Dexedrine spansule, Lisdexamfetamine (Vyvance)

Methylphenidate Preparations

- Short- acting:
  Focalin, Methylin, Ritalin
- Intermediate-acting:
  Metadate ER, Methlyn ER, Ritalin SR, Metadate CD, Ritalin LA
- Long- acting:
  Concerta, Daytrana patch, Focalin XR

Methylphenidate			
Immediate release (IR)			
Methylphenidate	Ritalin[a]	Tablet	5, 10, 20 mg
		Chewable tablet	2.5, 5, 10 mg
	Methylin solution[a]	Oral solution	5 mg/5 mL, 10 mg/5 mL
Dexmethylphenidate	Focalin[a]	Tablet	2.5, 5, 10 mg
Extended release (ER)			
Methylphenidate	Ritalin LA[a]	ER capsule (50%IR: 50%ER)	10, 20, 30, 40 mg
	Metadate CD[a]	ER capsule (30% IR: 70% ER)	10, 20, 30, 40, 50, 60 mg
	Aptensio XR	ER capsule (40% IR: 60% ER)	10, 15, 20, 30, 40, 50, 60 mg
	Adhansia XR	ER capsule (20% IR: 80% ER)	25, 35, 45, 55, 70, 85 mg
		ER tablet[a]	20 mg
	Concerta[a]	OROS tablet	18, 36, 54 mg

	Brand	Form	Strengths
	Cotempla XR-ODT	ODT tablet (25% IR:75% ER)	8.6, 17.3, 25.9 mg
	Quillichew ER	Chewable tablet (30% IR,70% ER)	20, 30, 40 mg tablets
	Quillivant XR	ER suspension	25 mg/5 mL
	Jornay PM	DR/ER capsule	20, 40, 60, 80, 100 mg
	Daytrana	Transdermal patch	10,15,20, 30 mg
Dexmethylphenidate	Focalin XR[a]	ER capsule	5, 10, 15, 20, 25, 30, 35, 40 mg
Amphetamine			
Immediate release			
AMP MAS (3:1 *d*-AMP to *l*-AMP)	Adderall[a]	Tablet	5, 7.5, 10, 12.5, 15, 20, 30 mg
AMP racemic (1:1 *d*-AMP to *l*-AMP)	Evekeo	Tablet	5, 10 mg
	Evekeo-ODT	ODT tablet	5, 10, 15, 20 mg

	Procentra	Oral solution	5 mg/5 mL
Extended release			
AMP MAS (3:1 *d*-AMP to *l*-AMP)	Adderall XR[a]	ER capsule	5, 10, 15, 20, 25, 30 mg
	Adzenys ER	ER suspension	1.25 mg/mL
	Adzenys XR-ODT	ER ODT tablet	3.1, 6.3, 9.4, 12.5, 15.7, 18.8 mg
	Dynavel XR	ER suspension	2.5 mg/mL
	Mydayis	ER capsule	12.5, 25, 37.5, 50 mg

	Brand	Form	Strengths
Dextroamphetamine[b]	Dexedrine[a]	ER capsule	5, 10 mg
	Vyvanse capsule	ER capsule	10, 20, 30, 40, 50, 60, 70 mg

- There is rarely a need to initiate treatment with IR and then transition to ER formulations

- Interindividual variability

Steingard et al. 2019

- With the exception of preschool children, treatment is usually started with an ER formulation

- Short-acting stimulants often used as initial treatment in small children (<16 kg)

- Treatment should be started at lower dose (2.5mg) in preschool, ASD and intellectual disability

Long- acting stimulants

- Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing

- But may have greater problematic effects on evening appetite and sleep

MPH IR

- Ritalin : 5, 10, 20 mg Tab
- Dose range: 0.3–2.0 mg/kg/day bid-tid
- Starting dose 2.5– 5 mg bid
- Increase dose by 5–10 mg/day (in divided doses) q week
- Onset 30–45 minutes
- Duration 3–4 hours
- Max dose 60 mg/day

Methylphenidate OROS

- Starting dose 18 mg qam
- Increase dose by 18 mg/day q week
- Onset 30–45 minutes
- Duration 10–12 hours
- Maximum dose: 72 mg/day; if > 40 kg up to 90 mg/day

MPH

- Recently, a formulation has been introduced that is given in the evening but does not release medication until the next morning and then lasts all day.

MPH

- Significant delays in absorption are well documented with IR and ER formulations by taking with food and appear to be greatest with high-fat meals
- It does not appear that taking with food have a significant impact on bioavailability
- IR MPH is absorbed rapidly
- Tmax, the time to achieve maximum concentration is generally 1.5–2 hours postdose

AMP

- Rapidly absorbed
- Typical onset of action 30–45 minutes after oral administration
- A slightly longer duration of clinical effect: 4–6 hours for IR formulations, 8–12 hours for most ER formulations, and up to 16 hours for the formulation Mydayis
- AMP is more potent than MPH
- Recommended doses of AMP are approximately one-half to two thirds the dose of MPH

(Markowitz and Patrick 2017)

Lisdexamfetamine

- Rapidly absorbed and then hydrolyzed in red blood cells, which liberates the active d-AMP from the lysine

Lisdexamphetamine

- Starting dose 30 mg qam
- Increase by 10–20 mg/day weekly
- Onset of response by 60–90 minutes
- Duration of response up to 13 hours
- Capsule can be opened, and contents can be mixed with a small amount of yogurt, water, or orange juice

Implications of Differences Between MPH and AMP

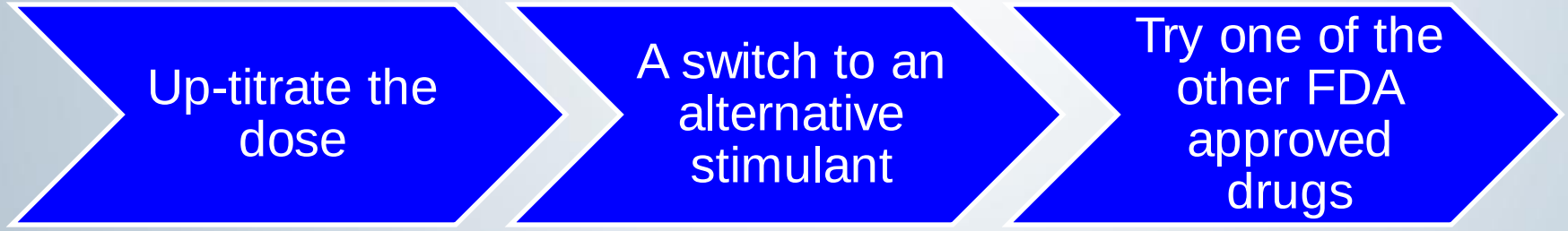
- Only about 40% of individuals will respond equally well to both stimulant compounds
- There are no reliable clinical or biological predictors of therapeutic response to or tolerability of a specific stimulant
- MPH may be the preferred drug for children and adolescents because of better tolerability

Stein et al. 2011, Cortese et al. 2018

If the treatment effect is “lost” over time

- Environmental factors (e.g., a behavioral response to new stressors)
- Developmental or maturational factors
- The emergence of a previously subthreshold comorbid disorder
- Nonadherence

If the treatment effect is “lost” over time



Side effects

- Decreased appetite
- Weight loss
- Insomnia
- Headache
- Tics
- Emotional lability/irritability
- Rebound phenomen
- Severe agitation or psychosis
- Exacerbation of Raynaud’s syndrome

- Individuals with Raynaud's syndrome can experience an exacerbation of symptoms (Coulombe et al. 2015)

- Hallucinations, a very rare side effect, typically remit when the drug is stopped (Coghill et al. 2014)

Effect on the Gastrointestinal System

- ↑ stomach acid production (heartburn and indigestion)
- ↓ appetite (stomach pain, nausea, and vomiting)
- Affect the normal movement of the GI (delayed gastric emptying, bloating, constipation)

Holmskov et al 2017

Effect on the Ocular System

- blurred vision
- dry eyes
- pupil dilation
- changes in intraocular pressure
- eye redness

✓ The exact mechanisms not fully understood

✓ Maybe impact on neurotransmitter levels(particularly DA and NE

Bingöl-Kiziltunc: 2013

Warning

These medications should generally **not be used** in children and adolescents with **preexisting heart disease** or symptoms suggesting significant cardiovascular disease.

This would include a history of severe palpitations, fainting, exercise intolerance not accounted for by obesity, or strong **family history of sudden death**.

- Mild changes in HR and BP can occur (average 6–8 bpm, 3–6 mm HG systolic BP, 3–4 mm HG diastolic BP)

Monitoring efficacy & safety

- Monitoring baseline heart rate (HR), blood pressure (BP), height, and weight

- Using one of a number of well validated scales (e.g., Conners 3, Vanderbilt Assessment Scales)

Stimulant treatment may be associated with a reduction in expected height gain at least in the first 1 to 3 years of treatment

- The American Academy of Pediatrics published a policy statement that an ECG is not routinely indicated prior to stimulant treatment in otherwise healthy youth

- Blood pressure and pulse should be monitored with stimulant treatment and may be of greater clinical significance in the treatment of adults with ADHD.

(Perrin et al. 2008)

- There is no evidence base to support the combined use of MPH with any AMP formulation, and this combination is not recommended

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
- Fatigue
- Constipation
- Dry mouth
- Hypotension
- Dizziness
- GI discomfort
- ECG changes : decreased HR, increased PR interval, and increase in QTcF
- Rebound hypertention

Noradrenergic Reuptake Inhibitors

- TCA
- Atomoxetine

Atomoxetine

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

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

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 algorithm 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

Stramox® 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.

Off-Label Medications

- Antidepressants

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

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

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

Modafinil

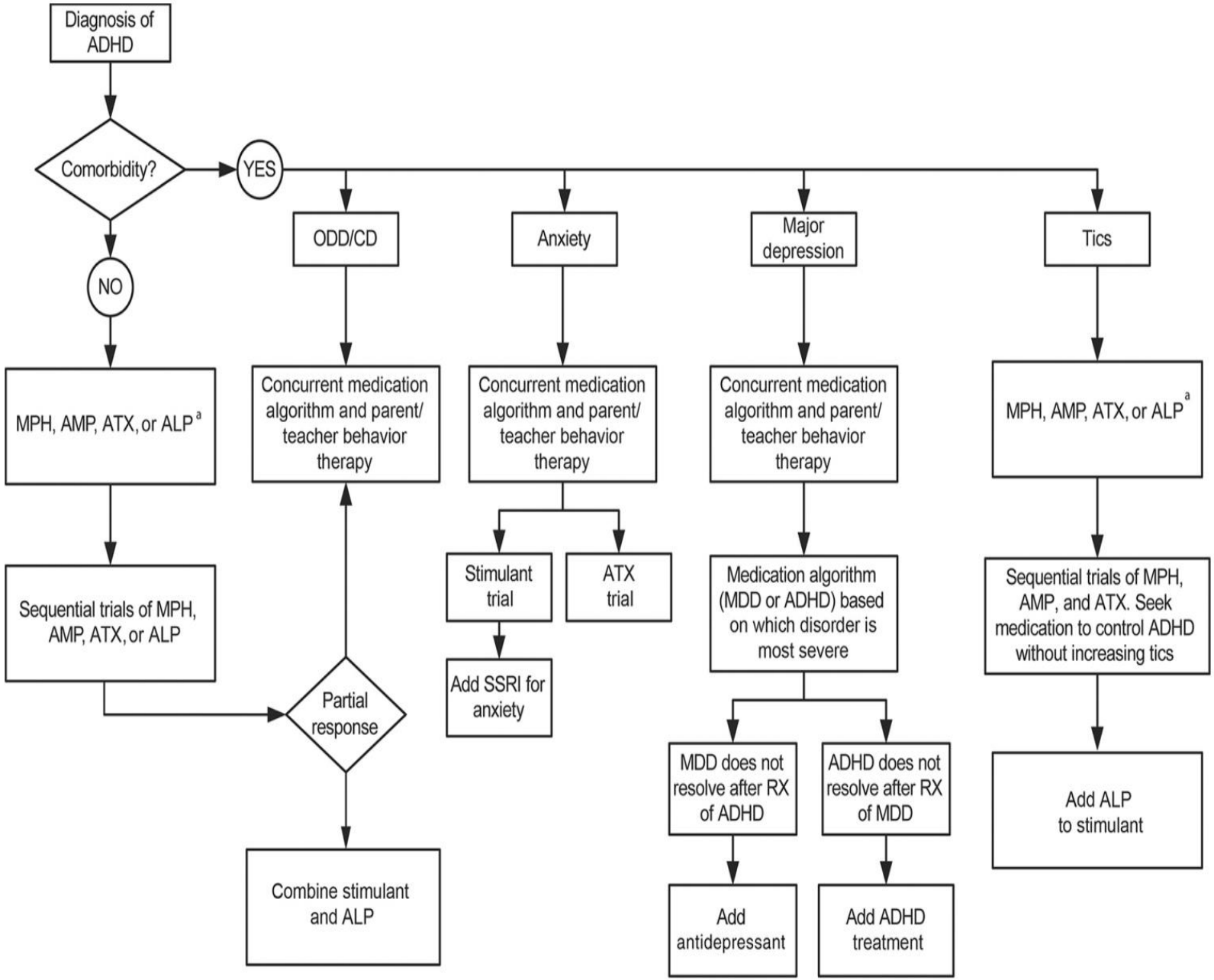
- ✓ It does not activate the areas of reward and abuse in the brain
- ✓ Increased efficacy with higher dosages(340-425mg/day)
- ✓ Significant improvement were observed in a large RCT by Biederman et al(2005)
- ✓ Risk of srious Stevens-Johnson-like rashes

New Agents

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

- The Schedule IV stimulant mazindol as well as centanafadine, a triple norepinephrine-dopamine-serotonin reuptake blocker

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]
Sequential trials of MPH, AMP, ATX, or ALP
Concurrent medication algorithm and parent/ teacher behavior therapy
Partial response
Combine stimulant and ALP
Concurrent medication algorithm and parent/ teacher behavior therapy
Stimulant trial
ATX trial
Add SSRI for anxiety
Concurrent medication algorithm and parent/ teacher behavior therapy
Medication algorithm (MDD or ADHD) based on which disorder is most severe
MDD does not resolve after RX of ADHD
ADHD does not resolve after RX of MDD
Add antidepressant
Add ADHD treatment
MPH, AMP, ATX, or ALP[a]
Sequential trials of MPH, AMP, and ATX. Seek medication to control ADHD without increasing tics
Add ALP to stimulant

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