Overview of ADHD Symptoms in ID/D

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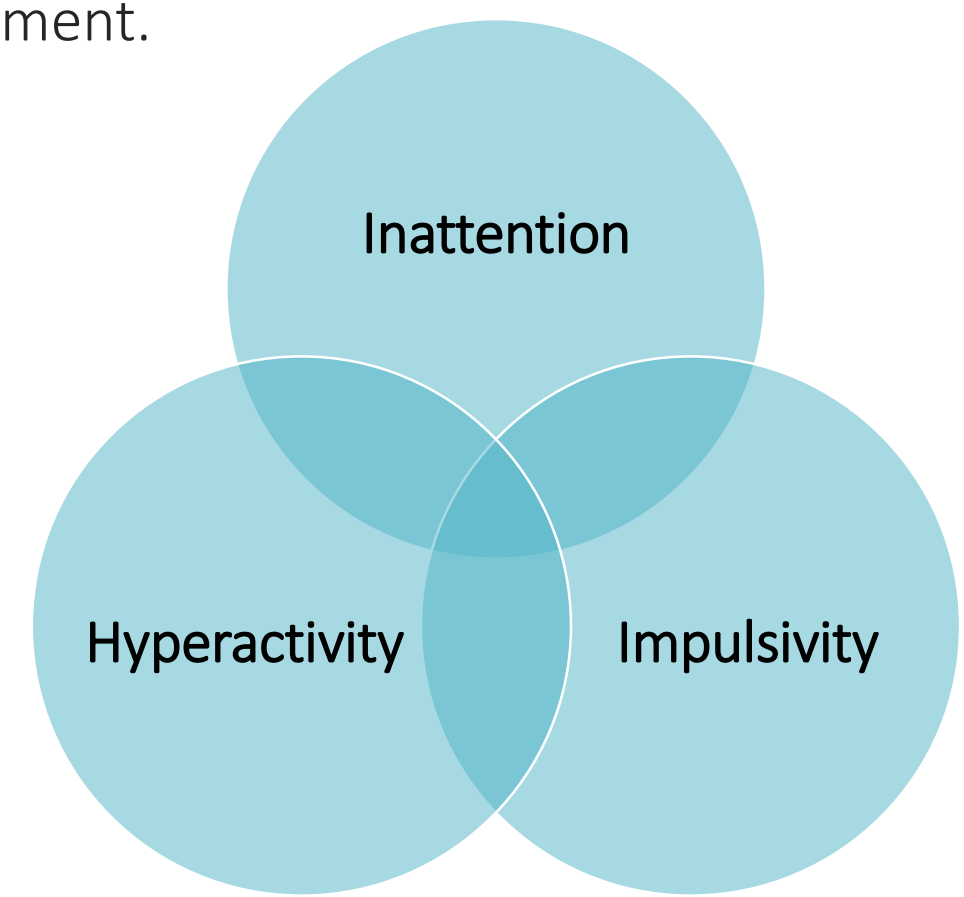
Objectives

Define	Define symptoms of ADHD, as defined by DSM-5
Learn	Learn about how ADHD and ASD/DD are biologically related.
Review	Review evidence-based medication strategies for treating ADHD symptoms
Discuss	Discuss evidence for non-medication treatment strategies

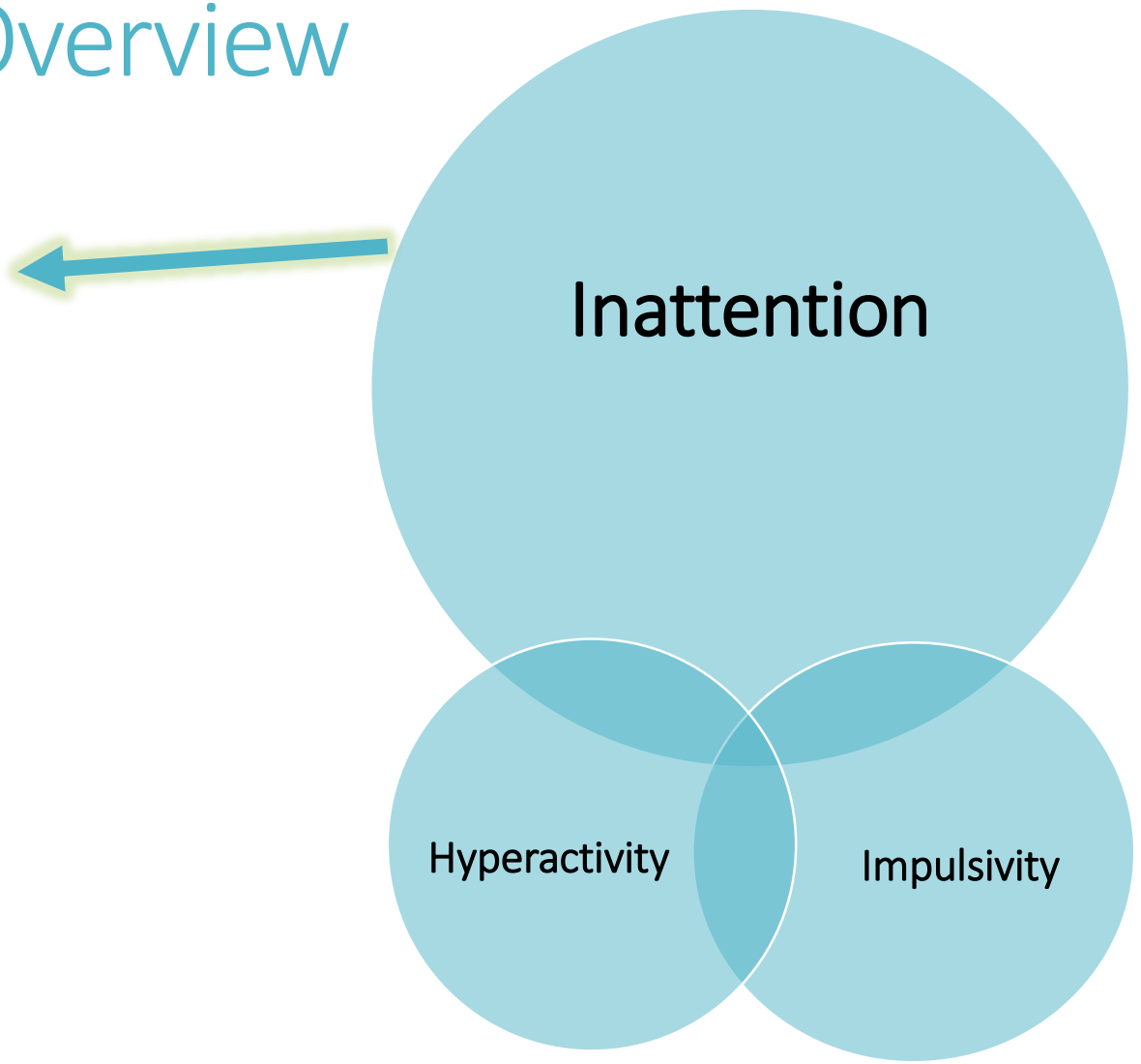
ADHD: DSM-5 Overview

A persistent pattern of **inattention** and/or **hyperactivity-impulsivity** that **interferes with functioning** or expected development.



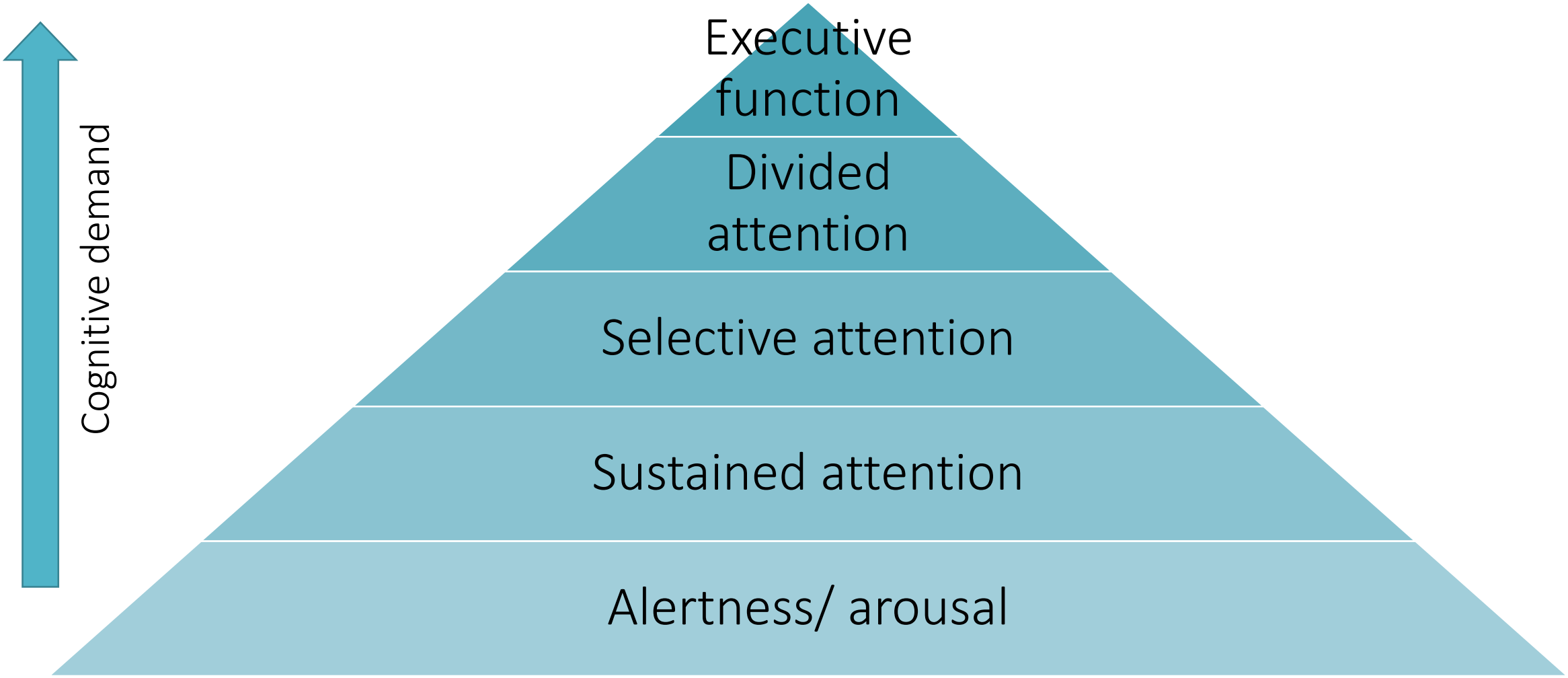
ADHD: DSM-5 Overview

- Fails to give close attention to details or makes careless mistakes
- Has trouble holding attention on tasks or play activities
- Often does not follow through on instructions and fails to finish schoolwork or chores.
- Has trouble organizing tasks and activities
- Avoids, dislikes, or reluctant to do tasks that require sustained mental effort
- Often loses necessary things
- Easily distracted
- Forgetful in daily activities

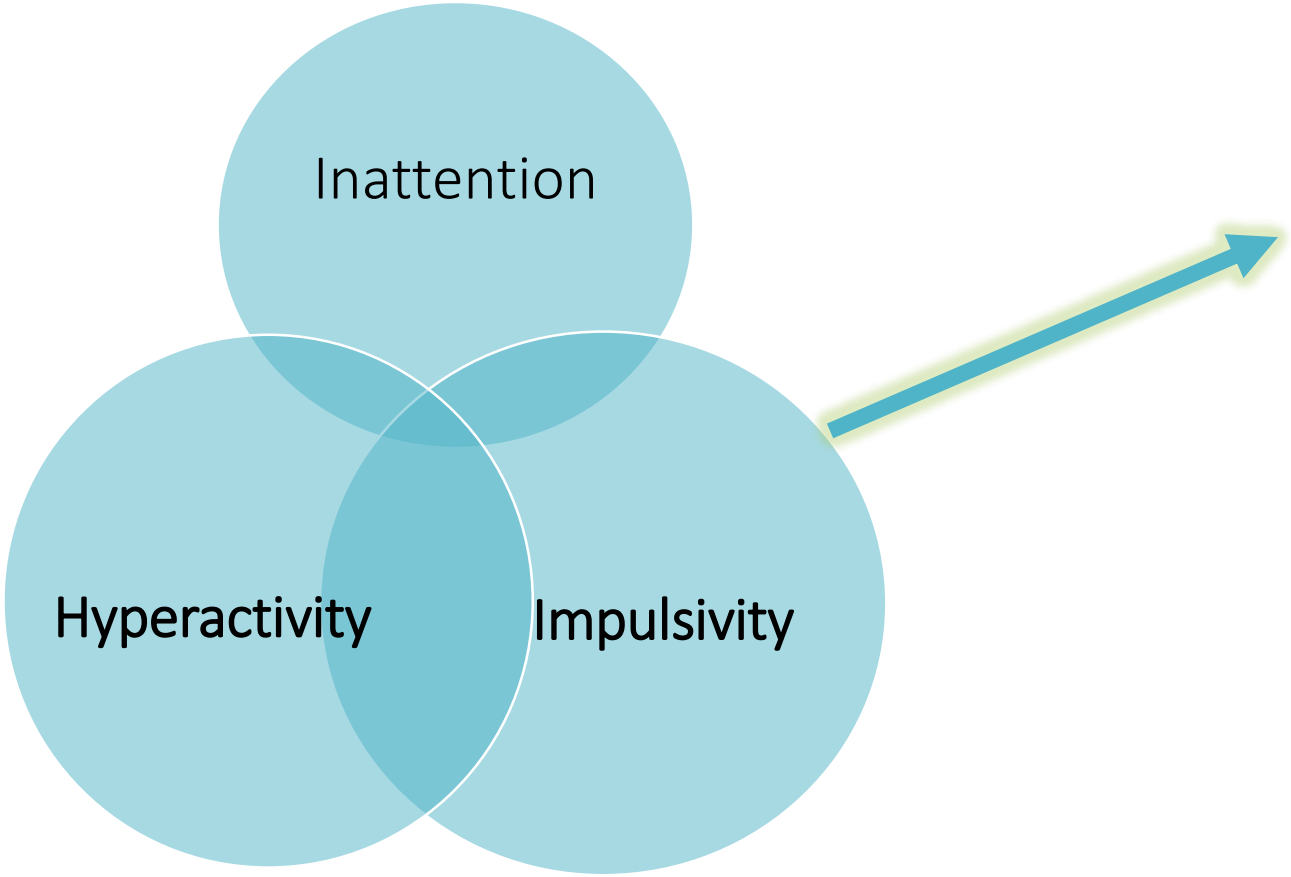


*Has ≥6 symptoms + **inappropriate for developmental level**

Hierarchy of attention



ADHD: DSM-5 Overview



Hyperactivity/ Impulsivity:

- Often fidgets or squirms in seat
- Often leaves seat when remaining seated is expected
- Often runs/ climbs about excessively, or often feels restless
- Often unable to play or participate in leisure activities quietly
- Often "on the go," or "driven by a motor"
- Talks/ vocalizes excessively
- Often blurts out answer before sentence is completed
- Has trouble waiting turn
- Often interrupts or intrudes on others

*Has ≥6 symptoms + **inappropriate for developmental level**

ADHD: DSM-5 Overview

- Symptoms must be present prior to age 12
- Symptoms present in at least 2 different settings (e.g., school, home, work)
- Clear evidence of interference with functioning or development

- Three possible presentations:

1. Inattentive subtype
2. Hyperactive-Impulsive subtype
3. Combined subtype

Tools to help establish the diagnosis

- **Vanderbilt Assessment Scales (Parent and Teacher)**
  - *Screens for ADHD, ODD, conduct problems, anxiety, academic problems*
- **Conners ADHD Rating Scale (Parent and Teacher)**
  - *Screens for ADHD and ODD symptoms*
- **Behavior Assessment System for Children, 3rd Edition (BASC-3)**
  - *Assesses an array of internalizing and externalizing behaviors*
- **In more complex cases, neuropsychological testing may be helpful.**
  - *Continuous performance tasks, tests of working memory and processing speed, executive functioning tasks*

*Currently, ADHD remains a clinical diagnosis based on a pattern of symptoms, with no established clinical biomarkers.

ADHD symptoms in I/DD are very common.

Prevalence rates in select neurodevelopmental disorders:

- **ASD**: approximately 50% (range: 30-80%)
- **Fragile X syndrome**: 65-85% in boys (inattention > hyperactivity)
- **Williams syndrome**: 84%
- **22q11 deletion (DiGeorge) syndrome**: 37%
- **Neurofibromatosis type 1**: 50-60%

Other conditions associated with ADHD+ASD

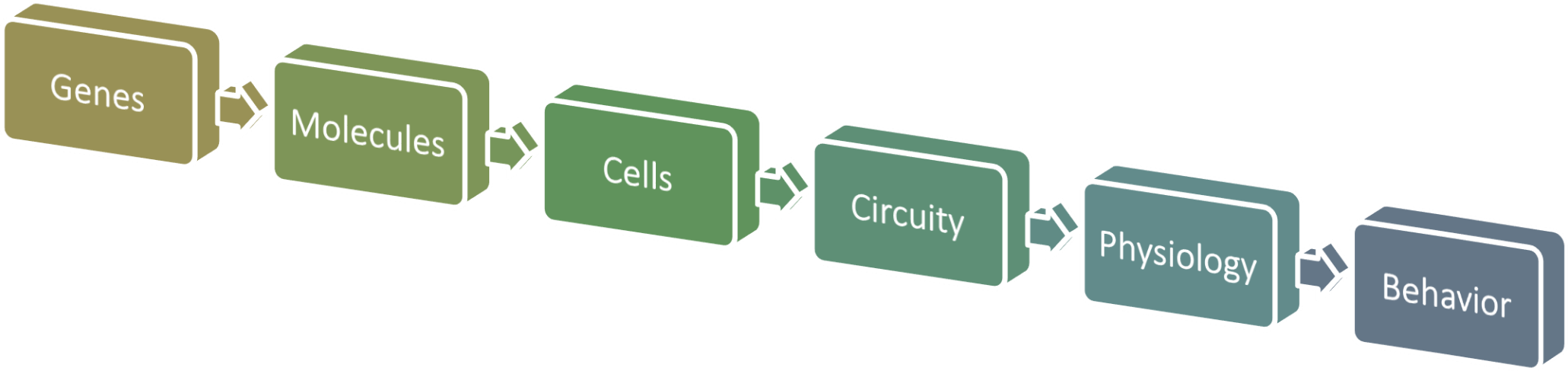
- Children with ASD diagnosed with ADHD are more likely to have:
  - *Intellectual disability*
  - *Motor delays*
  - *Enuresis*
  - *Allergies*
  - *Co-occurring Oppositional Defiant Disorder*
  - *Sleep disturbance*
  - *Anxiety*

Topic of debate: Are these separate ("comorbid") disorders, or should we consider ADHD symptoms a feature of the neurodevelopmental disorder?

How exactly are they related?

Does ADHD exist on a continuum with other disorders, such as ASD?

How can we approach this question?

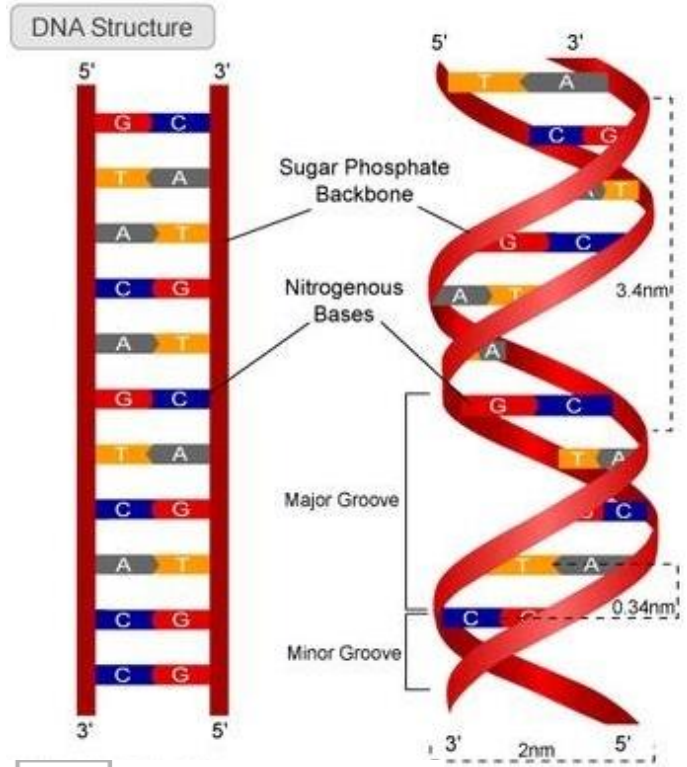


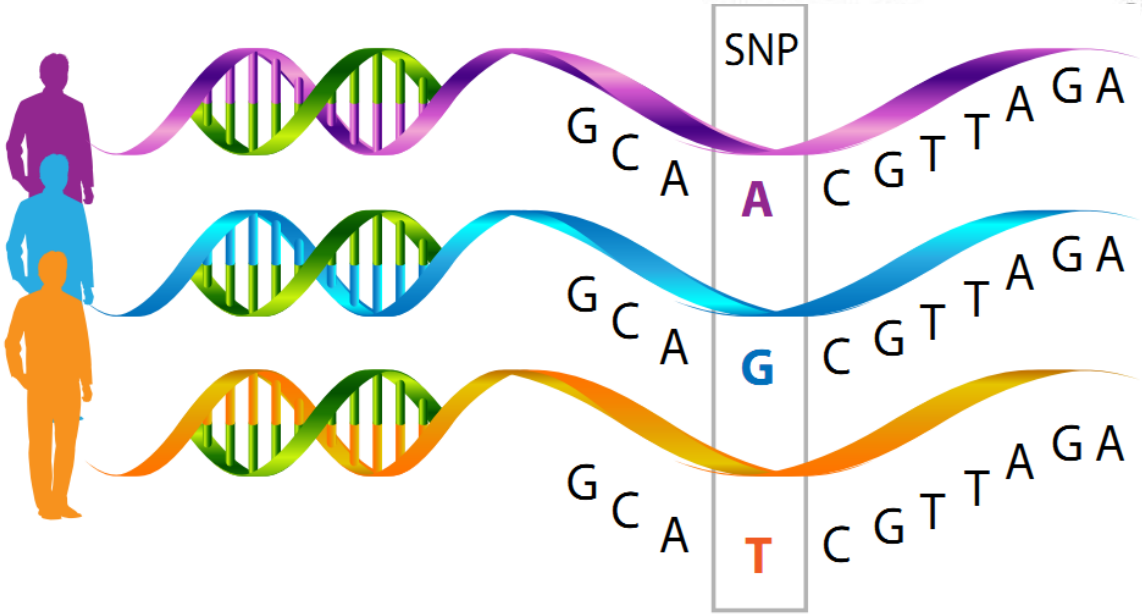
National Institute of Mental Health (NIMH)
Research Domain Criteria (RDoC)
Units of Analysis

How can we study genetic influences?

- Family studies
- Twin studies
- Genetic loci of interest / linkage studies
- Rare, single gene, disease-causing mutations
- Smaller, more common genetic variations that may play a causative role
  - Single nucleotide polymorphisms (SNPs)
  - Copy number variants (CNVs)
- Genome-wide association studies GWAS)

*Most cases of ASD and ADHD probably caused by many genes of small individual effect





What have we learned from genetic studies?

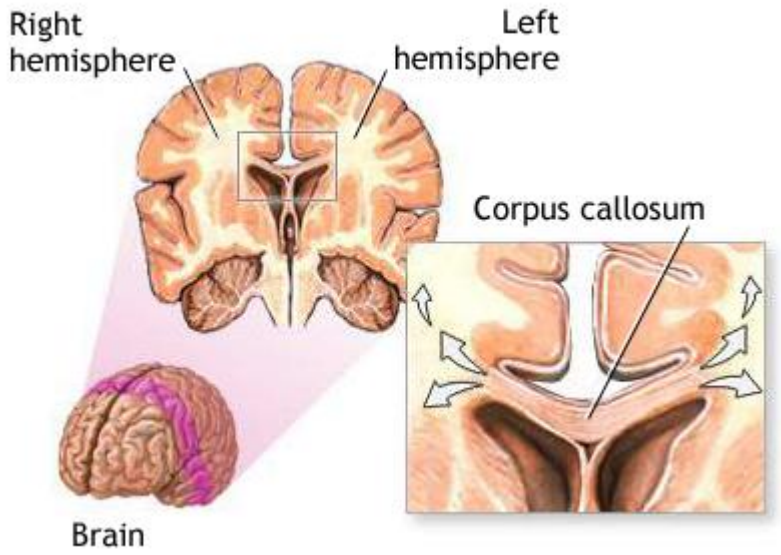
ADHD and ASD may share an underlying genetic basis:

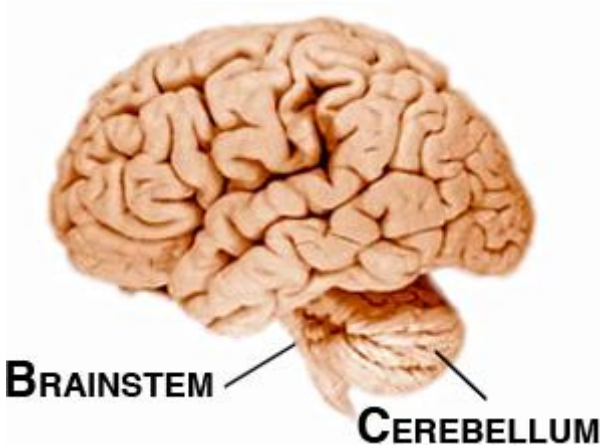
- Family studies: Children with ADHD and their sibs have higher ratings on ASD scales than controls. ADHD also more common in ASD families.
- Twin studies: Moderate to large genetic correlation between ASD and ADHD (50-72% attributable to genetic influences)
- Candidate gene studies: Weak evidence for polymorphisms in COMT, MAOA genes in both ADHD and ASD. Both associated with FMRI1 premutation (Fragile X "carrier"), 15q duplications, and 22q11 deletion.
- GWAS and linkage studies: Some evidence for overlapping Copy Number Variants (CNVs), genetic loci, and single nucleotide polymorphisms (SNPs) in ADHD and ASD. Cross-diagnostic research still limited.

Rommelse, Eur Child Adolesc Psychiatry (2010)

What have we learned from studies of brain structure?

- Structural imaging studies: use **MRI** to compare differences in brain anatomy: gray matter and white matter volumes, relative size and appearance of brain structures
- Strongest areas of overlap in **corpus callosum** and **cerebellum**: smaller volumes, reduced white matter integrity





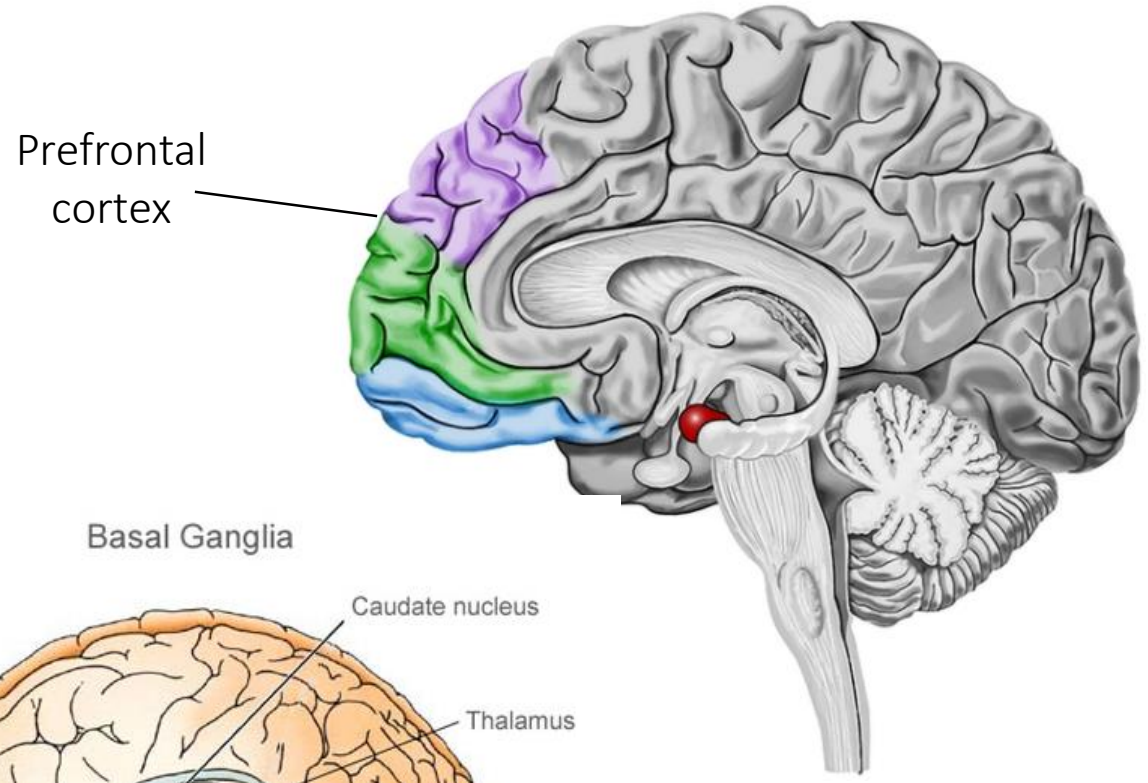
Dougherty et al; Neuropsychol Rev; 2016

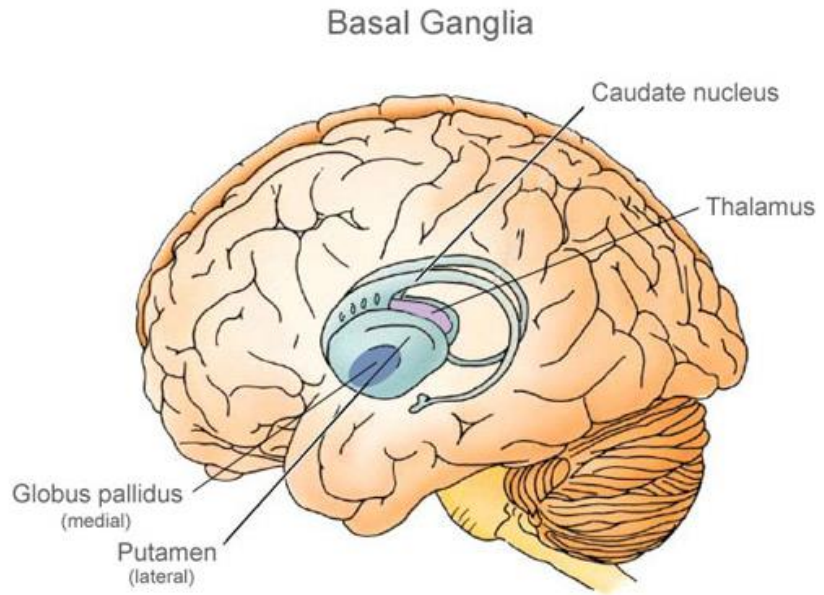
What have we learned from studies of brain structure?

Other areas of overlap:

- **Prefrontal cortex**: reduced volume in ADHD; abnormalities in gray and white matter in both (to different extents)
- **Caudate**: Overgrowth in ASD, decreased volume in ADHD
- **Overall brain volume**: increased in ASD (early in development), decreased in ADHD (delayed maturation)
- Widespread **white matter** abnormalities (inconsistent in studies)

(Ameis et al; Am J Psychiatary; 2016)





What have we learned from studies of neural circuits?

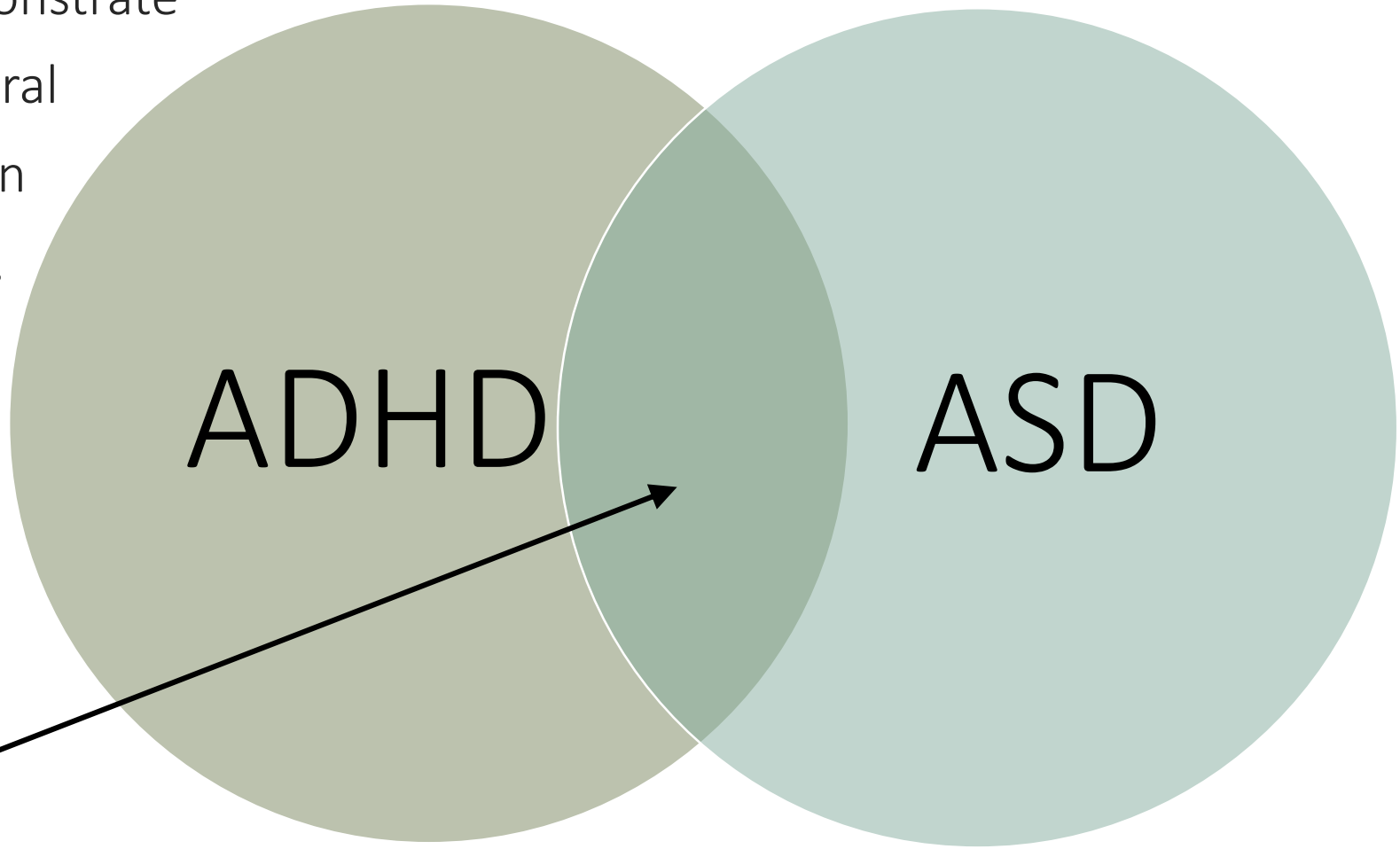
Functional imaging studies: Looking at how neural circuits or networks work together to perform a task

- In ASD: emerging evidence for long-range underconnectivity and local overconnectivity. May be present in ADHD as well.
- In ADHD: Deficits in fronto-striatal networks and decreased global efficiency of brain networks

What have we learned from studies of behavior?

Clinical studies demonstrate overlapping behavioral symptoms in children with ADHD and ASD.

- Social impairment
- Sensory processing differences
- Executive functioning deficits
- Impaired emotion regulation
- Motor functioning
- Sleep disturbance



Putting it all together…

- Individual behaviors exist on a continuum, ranging from normal to pathological.
- Features of ADHD common in ASD, and features of ASD common in ADHD.
- Family studies and genetic studies suggest some shared underlying genetic risk. Overlapping "epigenetic" effects are also possible.
- Brain imaging studies suggest certain brain regions and patterns of connectivity implicated in both: corpus callosum, cerebellum, basal ganglia, and long-range white matter tracts.
- Both disorders share neuropsychological features that are not part of the diagnostic criteria.
- Disruption of early neural connections may be a common causative factor in ADHD and other neurodevelopmental disorders.
- Future research studies may be more revealing if focused on brain-symptom connections rather than brain-diagnosis connections.

Why and when to treat

The case for treatment:

- ADHD symptoms associated with greater risk for academic and social problems (above and beyond ASD)
- Hyperactivity and impulsivity can present safety risks (e.g., climbing and jumping from heights, darting into streets)
- Symptoms can interfere with other developmental therapies

When to consider treatment:

- Symptoms are causing significant distress or functional impairment
- Symptoms cause safety risk
- Behaviors are outside normal range for **developmental** level and interfering with developmental progress

Other factors impacting attention and motor activity in ASD/ ID

- Decreased salience of social stimuli
- Increased attention to unique interests, own thought processes
- Decreased motivation for academic tasks- may not understand the value or purpose of the activity
- Sensory-seeking behavior (i.e., movement seeking)

Case Example: ADHD symptoms in I/DD

KT is a 7-year-old boy with autism, intellectual disability, and no expressive language. He is almost always in constant motion, including pacing, flicking objects, shaking strings, humming, climbing, and jumping off furniture. At school, he will sometimes run away from the classroom, particularly during activities that he finds boring or challenging. He has little safety awareness and will dart off in parking lots and stores unless his parents' hold his hand. KT has never sat through an entire family meal at home, preferring to "graze" and walk around while eating. At school, he is able to sustain his focus on a task for no more than 5 minutes, even with the support of a teacher's aide, incentives, and use of a visual timer. His mother notes that he only stops moving when he's sick or asleep. Bedtime is very difficult, as he has a lot of trouble settling for sleep, and he will sometimes wake up in the middle of the night and start playing with his toys. His parents have installed deadbolt locks at the tops of their doors and alarms on the windows for safety.

Treatment Options for ADHD Symptoms

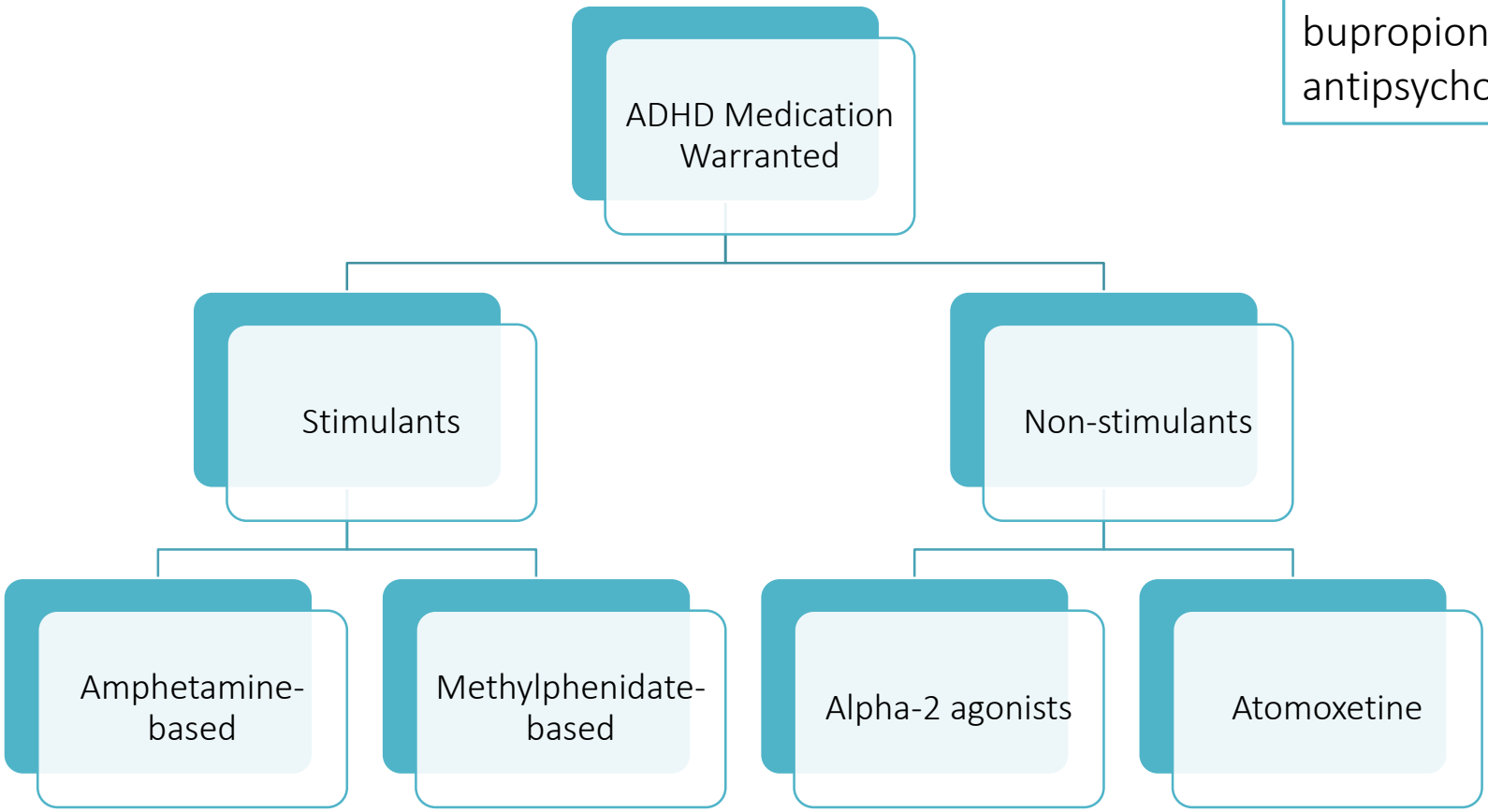
- No medications specific to ADHD in ID/D (we use meds approved for ADHD).
- For most, pharmacotherapy (medication) is first-line treatment for ADHD. Behavioral therapy is first-line for most preschool-aged children.
- However, combination of medication + parent-child behavioral therapy may improve some related symptoms (e.g., aggression, oppositional behavior, compliance).
- Environmental and home supports/ accommodations are also helpful.
- Individual therapy (CBT) may be helpful for associated psychological symptoms (eg, anxiety), but not core ADHD symptoms.
- Physical exercise (at least 60 min day) also important!

Questions to consider before medication treatment

- Are symptoms of inattention, hyperactivity, and impulsivity above and beyond what would be expected for another child of a similar developmental level?
- Are expectations for the child's performance realistic?
- Is there functional impairment in more than 2 settings?
- Could medical or other psychiatric problems be affecting attention?
  E.g., Absence seizures, sleep disturbance, anxiety
- Could medications be affecting attention?
  E.g., Topiramate, antipsychotics, SSRIs, antihistamines

ADHD Treatment Options

*None specifically approved for use in ASD or ID
*Third line options include: bupropion, atypical antipsychotics, amantadine

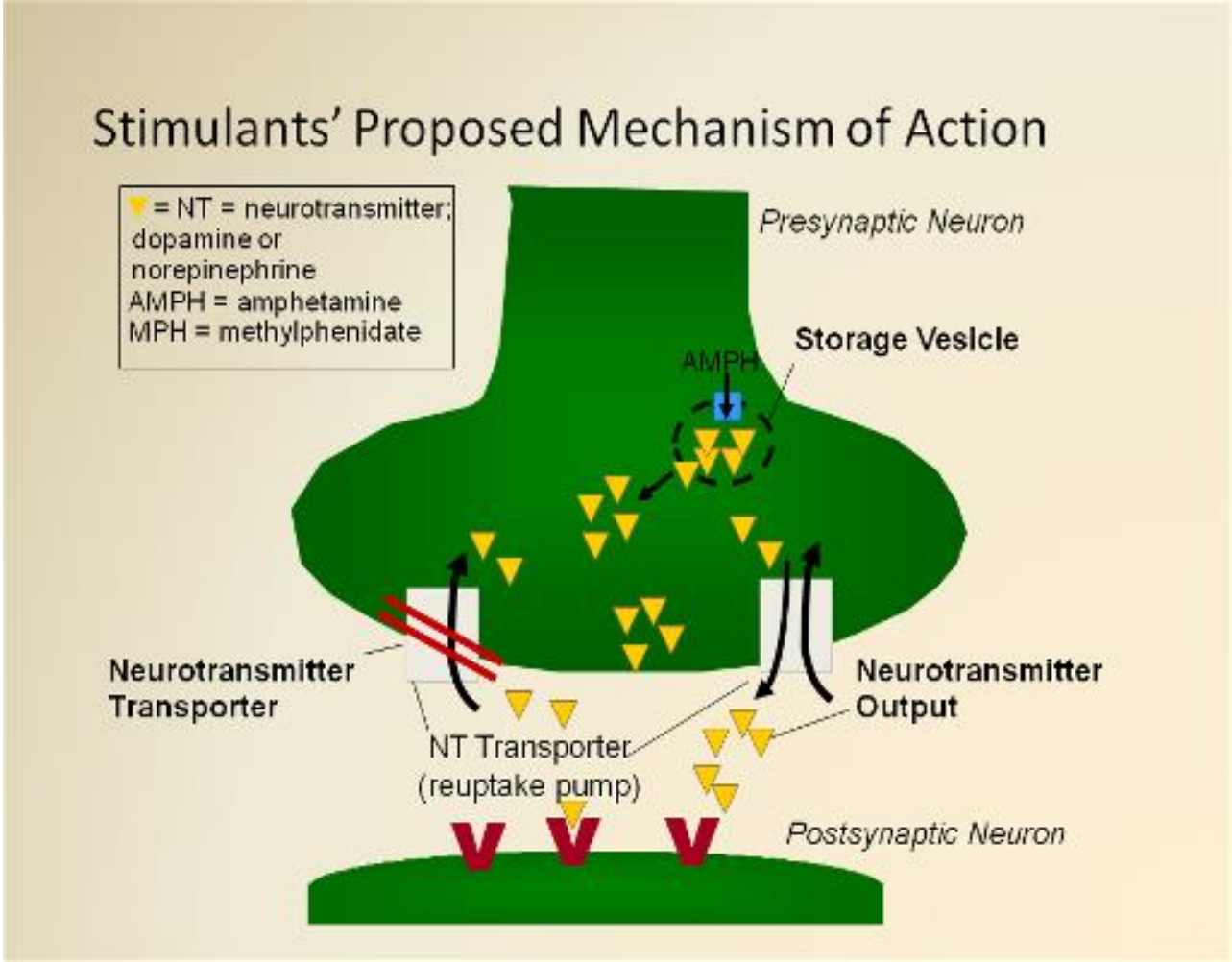


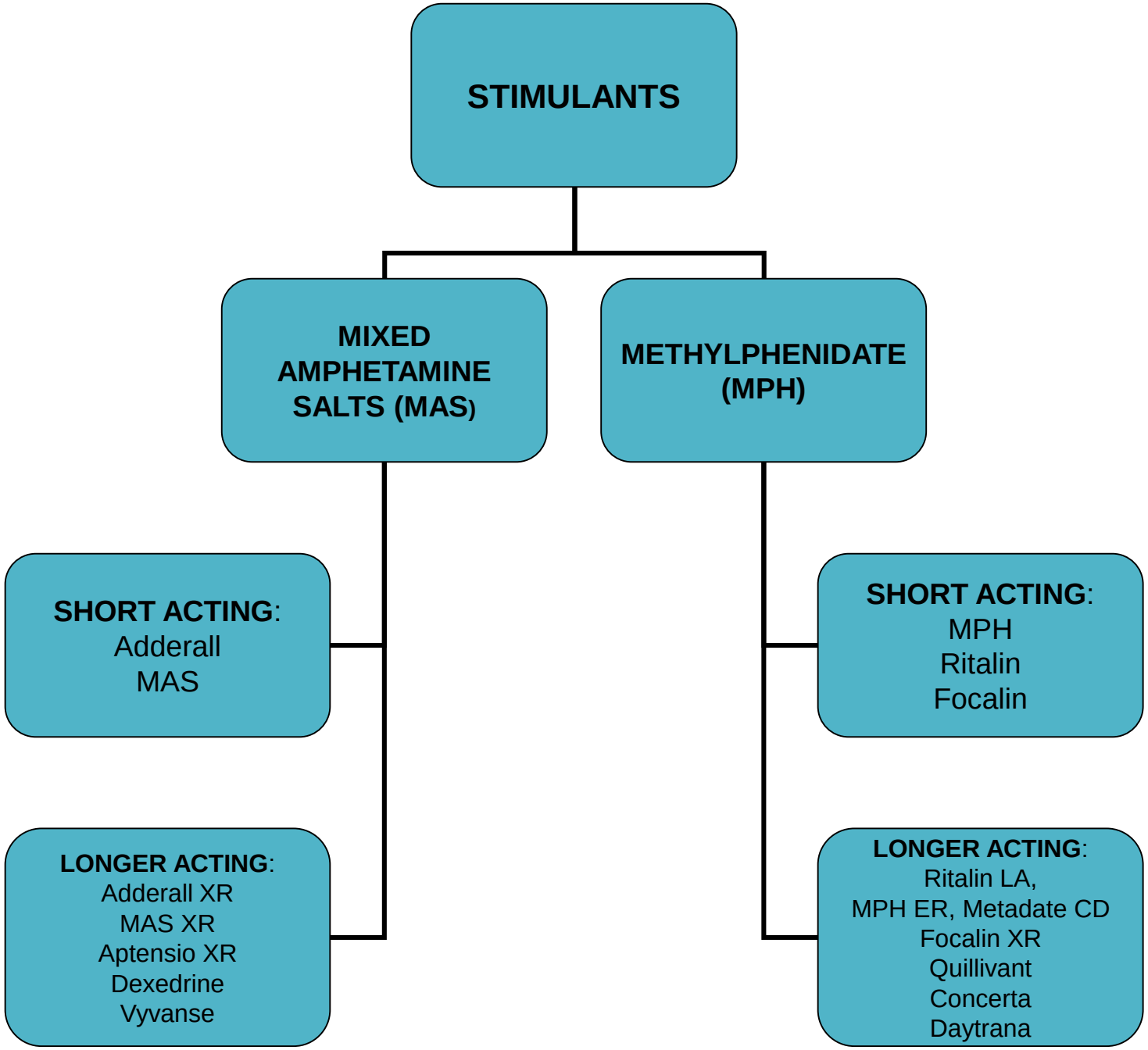
Stimulant medications

- First choice for most
- Two classes: methylphenidate and amphetamine-based
- Short-acting (2-4 hr), intermediate (6-8 hr), and long-acting (10-12 hr)
- Differences in release profiles

("single hump" vs "double hump")

- May respond better to one class vs another, though difficult to predict; may require >1 trial




STIMULANTS
MIXED AMPHETAMINE SALTS (MAS)
METHYLPHENIDATE (MPH)
SHORT ACTING:
Adderall
MAS
LONGER ACTING:
Adderall XR
MAS XR
Aptensio XR
Dexedrine
Vyvanse
SHORT ACTING:
MPH
Ritalin
Focalin
LONGER ACTING:
Ritalin LA,
MPH ER, Metadate CD
Focalin XR
Quillivant
Concerta
Daytrana

Considerations in choosing a stimulant

- Age of child
- Goals of treatment
- Baseline appetite and sleep habits
- Formulation needs (e.g., capsules, liquid solution, patch)
- Co-existing medical problems (congenital heart defects, arrhythmias, underweight)
- Prior experiences with ADHD medications
- Family history of response to ADHD medications

Potential risks and benefits with stimulants

BENEFITS

- Quick onset
- Relatively easy to determine effects
- Well-studied in children
- Safe
- Usually well-tolerated
- Many choices to customize treatment
- Most effective meds for inattention

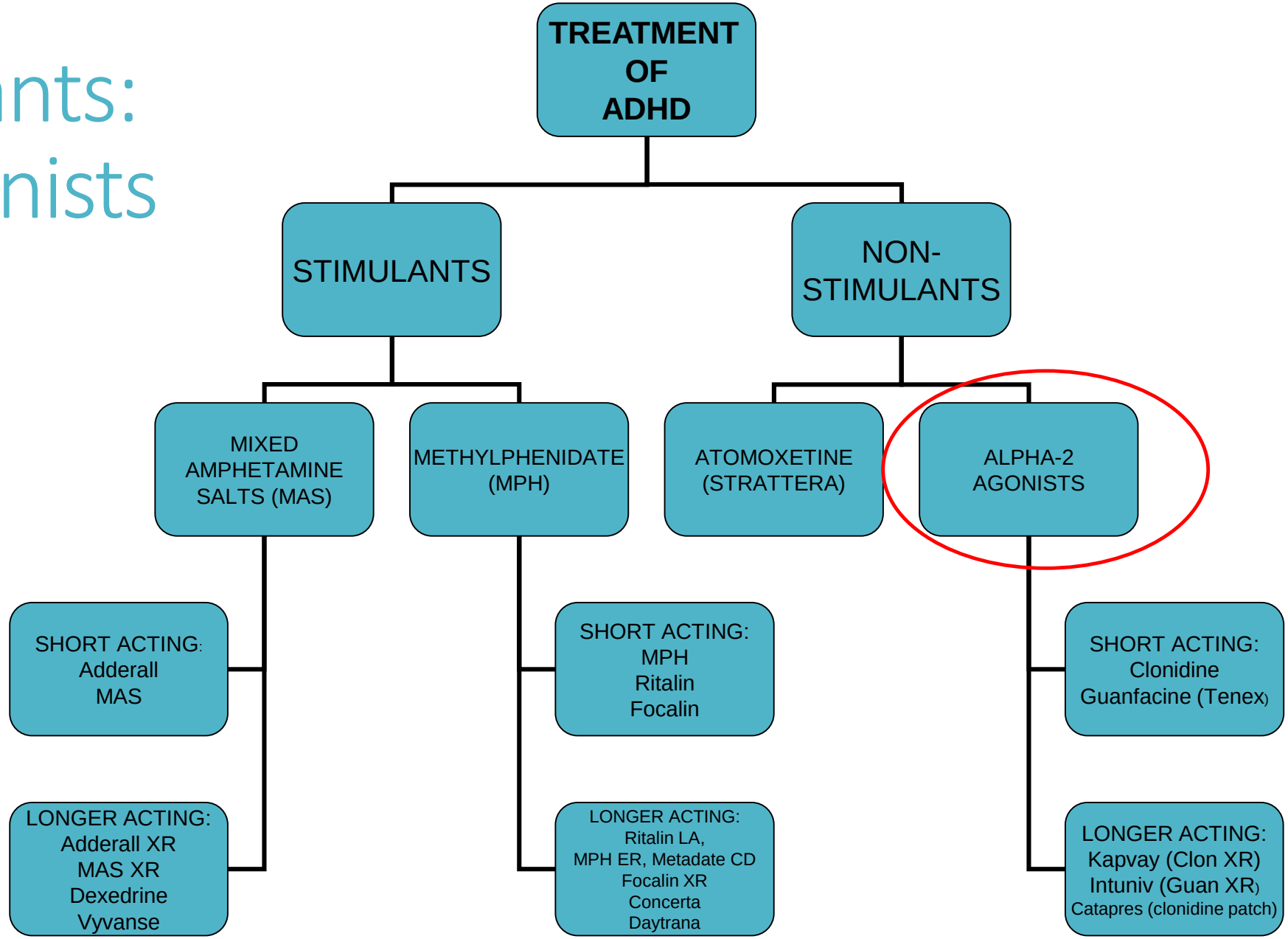
RISKS/ POSSIBLE SIDE EFFECTS

- Lower appetite/ weight loss
- Insomnia
- Stomachache
- Headache
- May worsen tics/ repetitive behavior
- Irritability
- Social withdrawal
- Increased heart rate/ blood pressure

Evidence for stimulants in ASD/ID

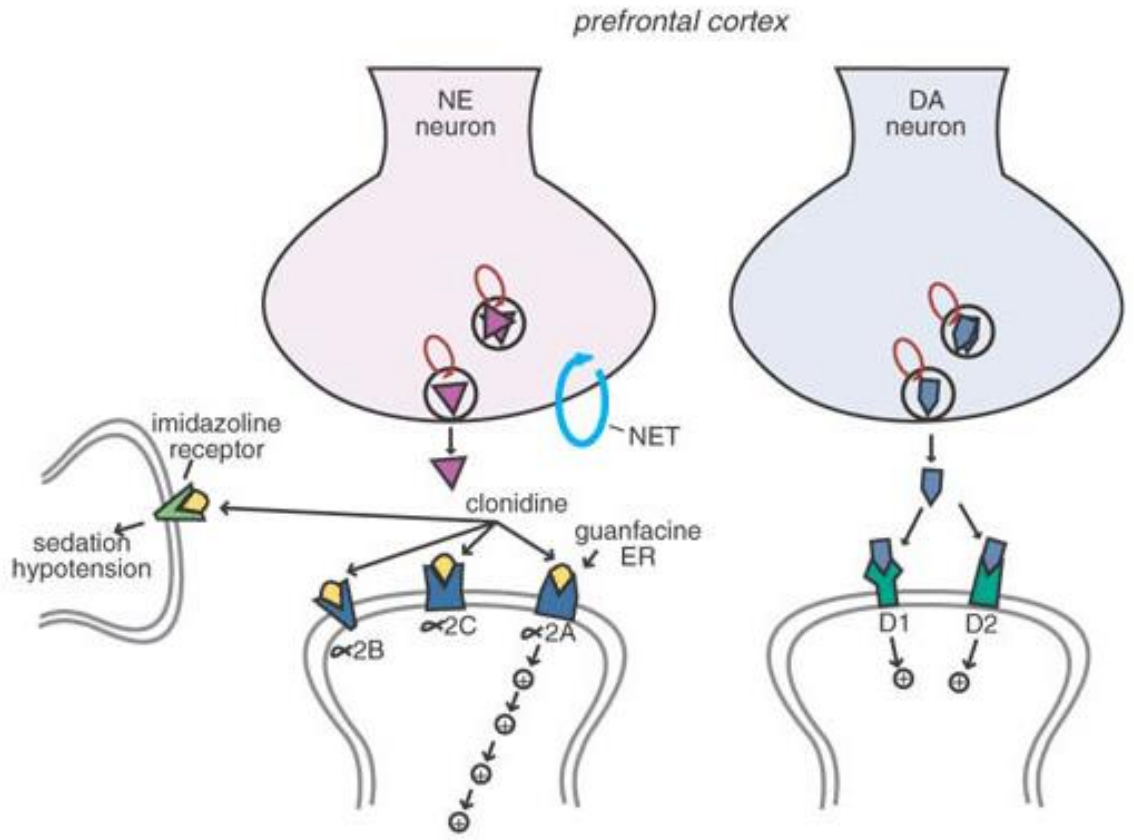
- Vast majority of studies with methylphenidate, not amphetamines
- Response rates lower than in ADHD without ASD (50% vs 80%)
- Rates of behavioral side effects (especially irritability, social withdrawal) higher (about 18% discontinued in 1 large study).
- Similar rates of lowered appetite and sleep changes (15%) compared with ADHD.
- Moderate to large effect sizes- slightly lower than in ADHD studies
- Response usually > for hyperactivity than attention.
- May respond best at lower doses than is typical in ADHD.
- Some studies show improvement in oppositional symptoms as well.

Non-stimulants: Alpha-2 agonists



Alpha-2 agonists: guanfacine and clonidine

- Mechanism of action: stimulate post-synaptic α_2 receptors in the pre-frontal cortex, potentiating norepinephrine (NE) transmission, strengthening PFC network connectivity.
- Guanfacine more selective than clonidine, causes less sedation and BP effects.
- Guanfacine extended-release (GEXR) and clonidine extended-release (Kapvay) FDA-approved to treat ADHD in children. Short-acting forms used off-label.
- In general, more effective for hyperactivity/ impulsivity than inattention.



Potential risks and benefits with alpha-2 agonists

BENEFITS

- Relatively quick onset
- Relatively easy to determine effects
- ER forms well-studied in children
- Safe
- Usually well-tolerated
- Less effects on appetite, sleep than stimulants
- Usually effective for hyperactivity and impulsivity

RISKS/ POSSIBLE SIDE EFFECTS

- Drowsiness/ fatigue
- Lowered heart rate, blood pressure
- Constipation
- Irritability
- No liquid formulations
- Short-acting tabs formulated for adult doses
- Less effective than stimulants for inattention

Evidence for alpha-2 agonists in ASD/ID

- Response rates for guanfacine ER about 50%, with large effect size for hyperactivity (Scahill et al; Am J Psychiatry, 2015)

  -No change in cognitive scores

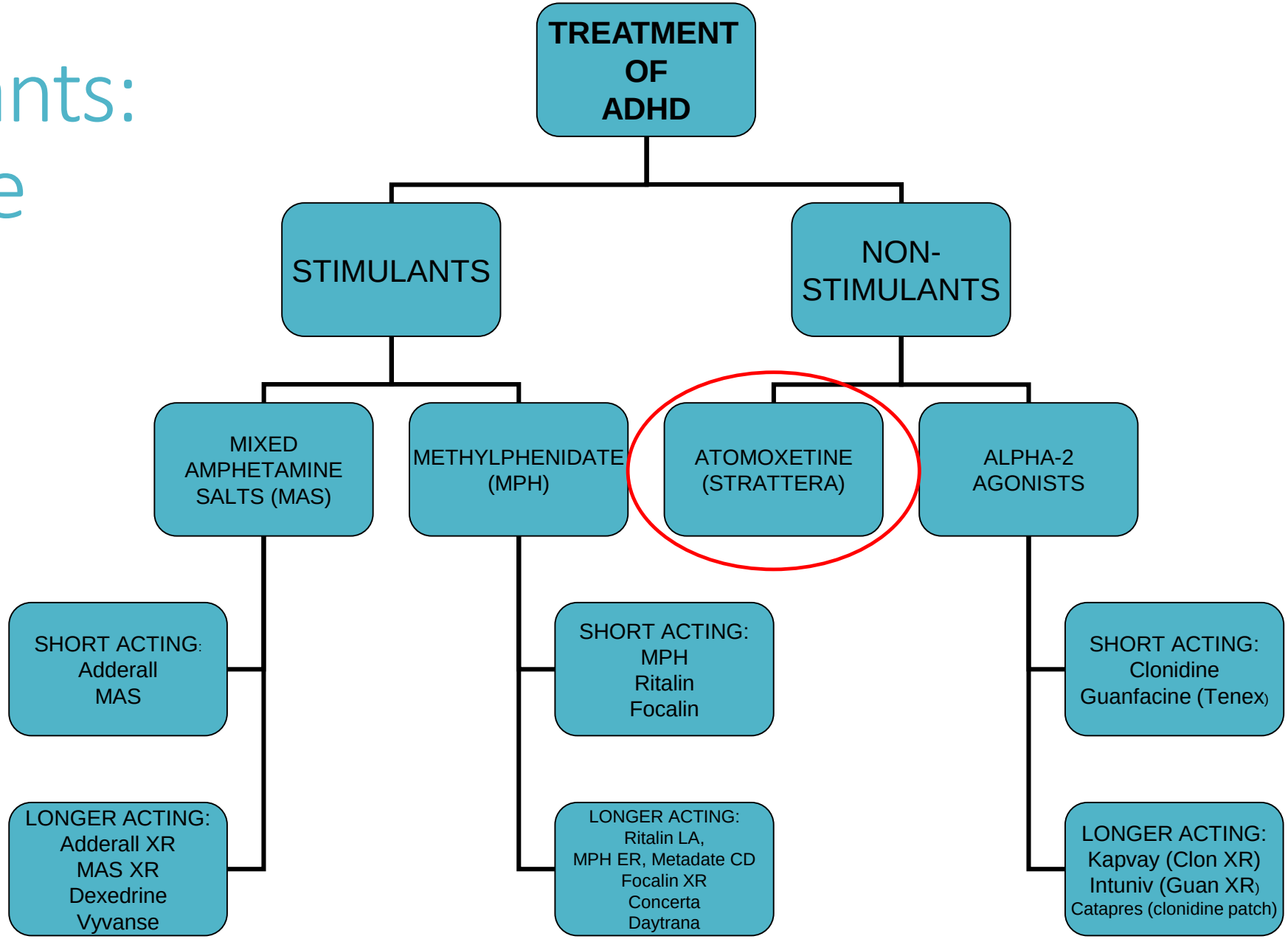
  -Significant difference in drowsiness, fatigue, decreased appetite, emotional/tearful, dry mouth, irritability, anxiety, and mid-cycle awakening.

  -Significant difference in incidence of ≥10-pt drop in diastolic BP; average decline in HR of 10 beats per minute. No EKG differences.

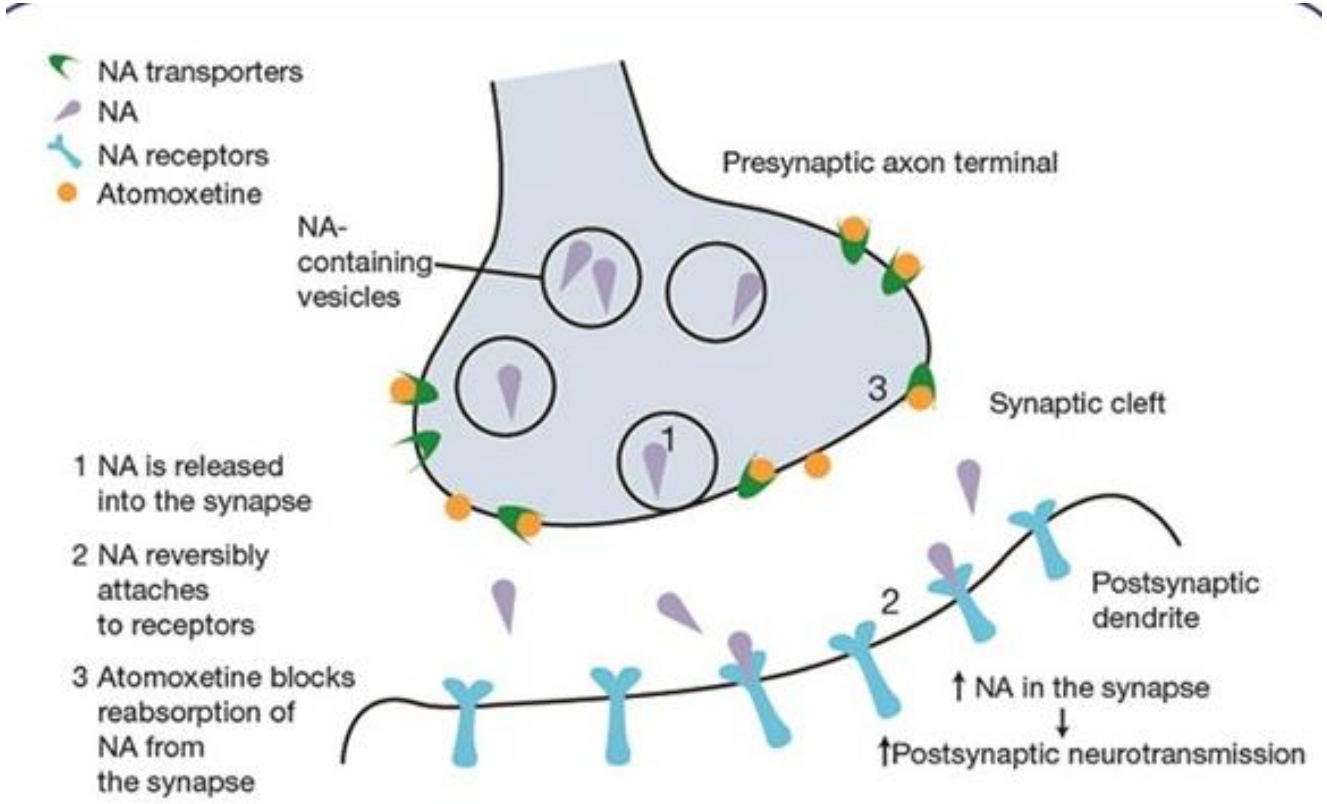
- Clonidine studies in ID/D generally small, sometimes no control groups.

- Sedation and hypotension more problematic with clonidine. Can be useful as a sleep aid.

Non-stimulants: Atomoxetine



Atomoxetine



Blocks re-uptake of norepinephrine into pre-synaptic neuron in pre-frontal cortex.

Potential risks and benefits with atomoxetine

BENEFITS

- Can be effective for attention as well as hyperactivity/ impulsivity
- Side effects generally mild
- May also reduce anxiety
- Safe
- Unlikely to worsen tics
- Less effects on appetite, sleep than stimulants (but still possible)

RISKS/ POSSIBLE SIDE EFFECTS

- Drowsiness/ fatigue
- Increased heart rate, blood pressure
- Nausea, stomach upset
- Capsule must be swallowed whole
- Rare risk of liver toxicity
- Possible risk of suicidal thoughts (uncommon)
- May take several weeks to see effects

Evidence for atomoxetine in ASD/ID

- Effects generally modest (similar to ADHD trials)
- Greater improvements in hyperactivity, though improvement also seen in concentration (Harfterkamp et al 2012)
- Common side effects: nausea, fatigue, lowered appetite, abdominal pain- tend to improve with time (similar rates to ADHD trials)
- Moderate improvements seen in non-compliant behavior (Handen et al 2014)

Off-label medication use for ADHD symptoms

- **Atypical antipsychotics** (risperidone, aripiprazole)
  - *-Effective for hyperactivity, BUT must balance against significant metabolic side effects*
  - *-Should not be used for inattention alone*
  - *-May be useful when significant irritability/ aggression also a problem*
- **Amantadine**
  - *-One clinical trial suggests effective in ASD; generally well-tolerated*
- **Bupropion**
  - *-May be useful when depression also problematic*
  - *-Can have stimulant-like side effects (lowered appetite, sleep disturbance, etc)*
- **Vayarin** (approved for use in ADHD)
  - *-"Medical food": EPA-rich omega-3 fatty acid + phosphatidyl choline*
  - *-No studies specifically in ASD*
  - *-Unlikely to have as robust effect as other approved ADHD medications*

Non-medication treatment for ADHD symptoms: School Accommodations

- Preferential seating
- Extended time for assignments/ tests
- Quiet, distraction-free space for testing and personal work
- Use of subtle prompts from teacher to re-focus (e.g., hand on shoulder)
- Movement breaks
- Fidgets/ sensory diet
- Use of visual supports (e.g., schedules, checklists)
- Graphic organizers
- "Chunking" of longer assignments into manageable parts
- Positive reinforcement for on-task behavior
- Access to calm-down space, if needed
- Social skills instruction, if needed

Other non-pharmacological treatments

Neurofeedback:

- "Training the brain" to increase fast wave (beta) activity and decrease slow wave (theta) activity through focused tasks with EEG-assisted feedback
- Difficult to design studies with minimal bias, large sample seizues
- Meta-analysis of 13 studies does not support efficacy in ADHD (Cortese et al 2016)

Cognitive training:

- Computerized or cognitive activities targeting attention, working memory, or inhibitory control, theoretically strengthening connections underlying these processes.
- Meta-analysis of 15 studies found minimal effects when raters were blinded to treatment (Cortese et al 2015)
- Performance on working memory tasks improved, but did not translate to academic performance

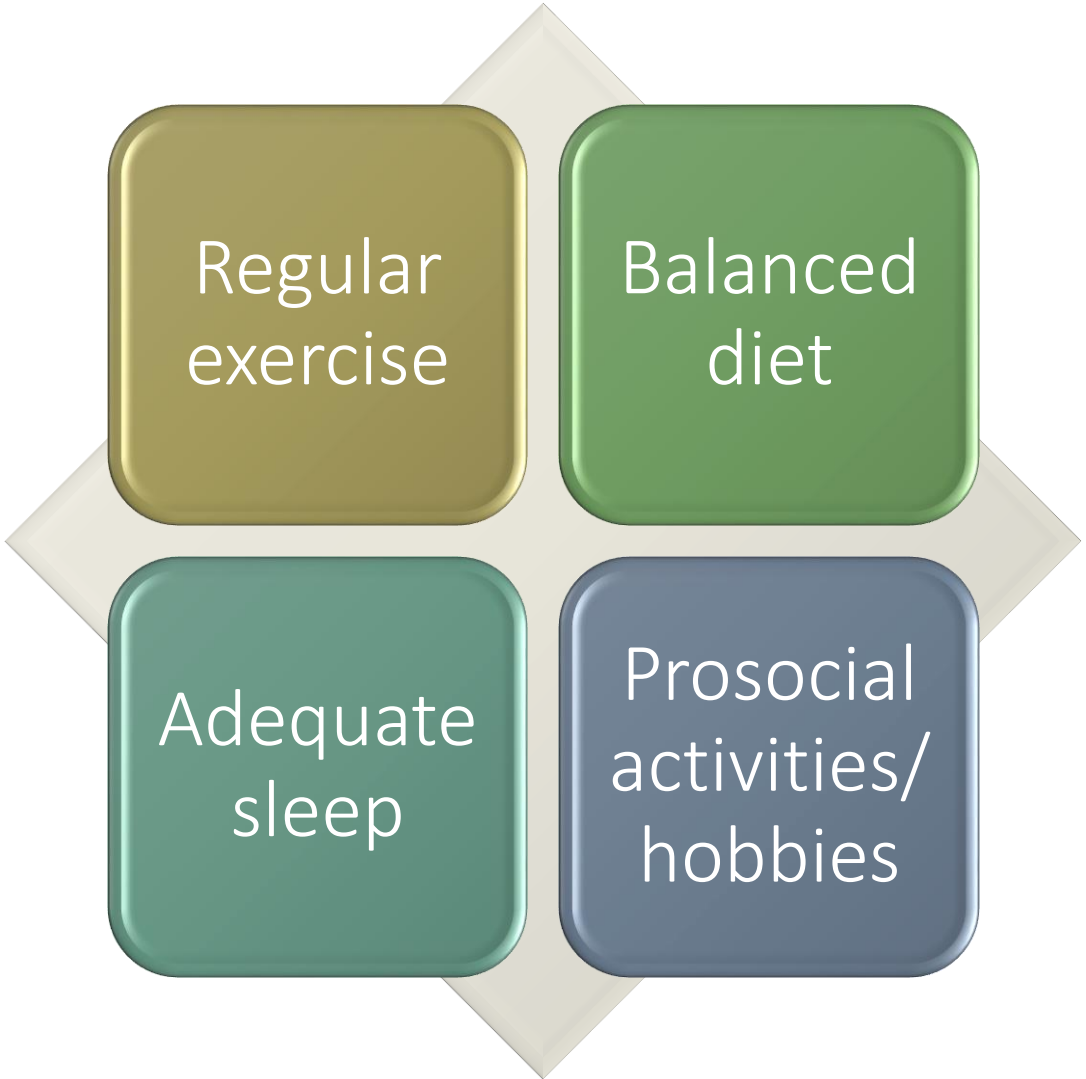
Elimination diets (e.g., artificial food dyes, gluten/ casein):

- No conclusive evidence to support recommendation, though may be useful for minority with food sensitivity

Parenting interventions:

- Guidance in using positive parenting techniques to manage challenging behaviors
- Improvements seen in conduct problems and oppositional behavior, but not core ADHD symptoms

Healthy habits to support well-being



Final Thoughts

- ADHD and ASD/ID commonly co-occur and cause significant impairment.
- ADHD and other NDDs may share underlying neurodevelopmental mechanisms.
- Symptoms need to be considered in context of developmental level.
- Medication is first-line treatment for core symptoms, especially methylphenidate, guanfacine, and atomoxetine.
- Behavioral interventions– especially behavioral/ parenting support and school accommodations– may improve functioning in combination with medication.
- Alternative treatments need further research
- Healthy lifestyle habits needed to support optimal functioning.

Thank you! Questions?