

**Psychopharmacological Approaches to the Treatment of Children & Adolescents with Autism & ADHD**

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**ASD & ADHD?**

- Symptoms of inattention, hyperactivity, impulsivity are common in individuals with autistic spectrum disorder (ASD)
  - Often the reason for clinical referral
  - Clearly established in the clinical literature
- However the current DSM (IV-TR) prohibits the diagnosis of attention deficit hyperactivity disorder (ADHD) in the presence of ASD
  - Many in the field realize that the diagnosis of ADHD in the presence of ASD clearly can be made.
  - Often later in life ADHD symptoms predominate in these individuals

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**ASD & ADHD?**

- Survey of 487 children/adolescents with ASD, >50% moderate to severe symptoms of inattention/hyperactivity-*(Lecavlier et al, 2006)*
- Sample of 101 children with ASD, 95% exhibited attentional deficits, 50% impulsive behavior & 75% symptoms consistent with ADHD- *(Goldstein, et al, 2004)*
- Presence of comorbid ADHD symptoms in children with ASD may predict greater impairment and activities of the daily life and higher rates of hospitalization- *(Frazier, et al., 2001)*

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## How to distinguish symptoms

- Individuals with ASD may exhibit selective inattention to social stimuli while sustaining focus on idiosyncratic interests are inanimate objects.
  - In contrast to the more pervasive distractibility present in uncomplicated (non-ASD) ADHD
  - Role of comorbid language issues complicates further
  - “Hyper focusing” as part of ADHD
  - Perseveration versus attentional problems

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## How to distinguish symptoms

- Overactivity/hyperactivity in ASD may be associated with motor stereotypies, anxiety, or agitation
  - Sensory seeking behavior (flopping on a couch, moving and stimming while watching TV) versus restlessness
  - Affect regulation difficulties almost impossible to separate
  - Relationship of anxiety with attention is particularly problematic and complicated
    - Anxiety can impair or improve attention depending on individual and other factors (baseline anxiety, baseline attention, presence of other learning issues, level of impulse control)

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## How to distinguish symptoms

- Similarly, some patients with ADHD symptoms and ASD fall more in the “ADHD camp,” others in the “ASD camp,” and yet others are not clear
- These “camp” considerations and other factors are relevant for selection of a possible medication
  - Level of cognitive functioning/language
  - Presence of other comorbidities especially anxiety and mood disorders
  - Known sensitivities or lack of sensitivity to medication is also relevant
  - Family history of response to certain medications

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## How to distinguish symptoms

- Similarly, these factors are relevant to possible medication related benefits/goals
  - Facilitate language/communication?
  - Improve attention?
  - Decrease hyperactivity?
  - Decrease impulse control problems, including difficulty with affect regulation?
  - Improve overall academic performance, social interaction, etc.

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## Medication options

- Psychostimulants
  - History of the drugs
  - Pharmacology of the drugs
  - New agents
- Nonstimulants
- Other drugs

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## Stimulants: History

- Amphetamine was first synthesized in 1887 by Lazar Edeleanu (University of Berlin)
  - Derived from plant derivative, Ephedrine
- Gordon Alles resynthesized the compound & introduced it to the world in the form of Benzedrine in 1927
- Methylphenidate (ritalin) developed in the 1950's but emerged prominently in the 1970's as a treatment for the disorder

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## Stimulants: History

- Since 1970's only **two** new medications for ADHD have been developed and approved
  - Strattera (atomoxetine)
  - Focalin (dexmethylphenidate)
    - a refined form of Ritalin\*, isolating only the centrally active isomer (d or dexmethylphenidate)
  - *Provigil (modifanil) was headed for approval but was NOT*
- The only other thing that has changed since that time is the PACKAGING (I.e. the delivery system) of the original molecules (methylphenidate, amphetamine)

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## Stimulant Mechanism of Action

- Despite name, psychostimulants do NOT cause "stimulation" when used at properly prescribed doses
  - When abused, much higher dose (often 100X (or more) typical prescribed dose)
  - Leads to very different effects/side effects
    - Euphoria
    - "High"
- Action does NOT result from "paradoxical effect"

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## Stimulant Mechanism of Action

- Methylphenidate and amphetamine both block the dopamine and norepinephrine transporters
  - Increase dopamine and norepinephrine in the synapse
  - Amphetamines also facilitate release as well
- Clinical efficacy of stimulants is likely correlated with synaptic dopamine and norepinephrine concentrations.<sup>1,2</sup>
- Impact on frontal circuits are the most relevant for positive impact on symptoms

1. Biederman J, Spencer T, *Biol Psychiatry*, 1999;46:1234-1242  
2. Schiffer WK, et.al. *aSynapse*. 2006;59:243-251

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## Reuptake Block Effects ADHD Symptoms

- Amplification of dopamine (DA) may improve performance in patients by decreasing distractibility or facilitating interest in the task.<sup>1</sup>
- Increasing postsynaptic norepinephrine (NE) may improve attention, alertness, vigilance, and executive function.<sup>2</sup>

1. Volkow, et.al. *J Neurosci*, 2001;21:RC 121  
2. Biederman J, Spencer T, *Biol Psychiatry*, 1999;46 1234-1242

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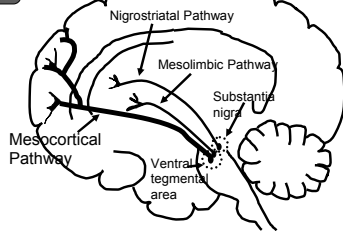
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## Dopamine Neurotransmission-ADHD

### Dopamine

- Enhances signal
- Improves attention
  - Focus
  - On-task behavior
  - On-task cognition



Solanto. *Stimulant Drugs and ADHD*. Oxford; 2001

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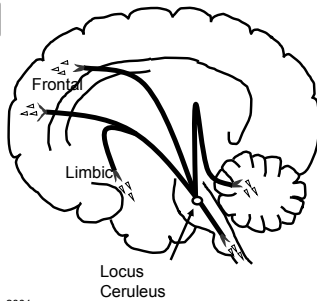
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## Norepinephrine Neurotransmission- ADHD

### Norepinephrine

- Dampens noise
- Executive operations
- Increases inhibition



Solanto. *Stimulant Drugs and ADHD*. Oxford; 2001.

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## Stimulants improve

- Core symptoms
  - Inattention
  - Impulsivity
  - hyperactivity
- Other symptoms
  - Noncompliance
  - Impulsive aggression
  - Social interaction
  - Academic efficiency
  - Academic accuracy
  - Family dynamics

ADHD Practice Parameters. J Am Acad Child Adolesc Psychiatry. 1997;36:85S.  
Greenhill LL, et al. J Am Acad Child Adolesc Psychiatry. 1999;38:503-512.

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## Stimulant side effects

### Limit dose efficacy

- Appetite decrease
- Weight loss.
- Insomnia

### Possible over time

- Nervousness/anxiety.
- Irritability.
- Dysphoria

### Transient/dose increase

- GI issues
- Headache

### Variable

- "Rebound"
  - Return of prior symptoms often to slightly higher level

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## Methylphenidates

### • Short acting

- Ritalin 2-4 hrs
- Focalin<sup>®</sup> 3-5 hrs

### • Long acting

- Metadate<sup>®</sup>CD 6-8 hrs
- Ritalin<sup>®</sup> LA 8-9 hrs
- Focalin<sup>®</sup> XR 10-12 hrs
- Concerta<sup>®</sup> 10-12 hrs
- Daytrana<sup>®</sup>(patch) 12+hrs

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## Amphetamines

- **Short Acting**
  - Dextroamphetamine
    - Dexedrine/Dexrostat 5-6 hrs
  - Mixed Salts
    - Adderrall<sup>®</sup> 6 hrs
- **Long Acting**
  - Mixed Salts
    - Adderrall XR<sup>™</sup> 8 hrs
  - Dextroamphetamine
    - Dexedrine Spansules 6-8hrs
    - Vyvanse 12 hrs

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## Extended Release Mechanisms

- First attempts(not really successful)
  - Ritalin-SR, Metadate ER, Dexedrine Spansules
- “Back Loaded”
  - Concerta (22/78),Metadate CD (30/70)
- Even Release (50/50)
  - Ritalin LA, Focalin XR
  - Adderrall XR
- Transdermal patch
  - Daytrana
- Prodrug
  - Vyvanse

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## Newer ADHD Medications

Concerta <sup>®</sup> :	methylphenidate formulated to mimic TID duration (12 hours)
Adderrall XR <sup>™</sup> :	extended-release formulation of mixed amphetamines (75% d-AMP) that mimics BID dosing (8-9 hours)
Ritalin <sup>®</sup> LA:	once-daily formulation of Ritalin <sup>®</sup> that mimics BID dosing and designed to last the school day (8-9 hrs)
Metadate <sup>®</sup> CD:	methylphenidate formulation designed to mimic BID duration (8-9 hours)

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## New ADHD Medications

Focalin <sup>®</sup> XR:	once-daily formulation of Focalin <sup>®</sup> that mimics BID dosing and designed to last 10-12 hrs
Strattera <sup>™</sup> :	selective norepinephrine reuptake inhibitor that can be dosed BID or QD
Daytrana <sup>™</sup> :	transdermal preparation of methylphenidate that offers flexibility of duration of action
Vyvanse <sup>™</sup> :	lisdexamfetamine dimesylate, prodrug of dextroamphetamine with longer duration (12 hrs)

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## Medication considerations

- These various options differ in amount and time of medication release
  - Can impact the timing and intensity of “rebound”
- Choice depends on individual needs of the patient
  - Sensitivity to specific side effects
  - Time in which greater symptom coverage is needed
- Longer acting agents are generally preferable.
  - More practical for patient/parent.
  - No need to get second dose, including at school

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## Medication considerations

- Daytrana transdermal patch
  - Useful for those individuals who cannot swallow.
  - Tactile/sensory issues may limit use in ASD
  - Can control time of onset and offset
- Associated side effects.
  - Anxiety/mood symptoms, sometimes more common with certain agents
- Sprinkle forms
  - Useful for those individuals who cannot swallow
  - Also allow more accurate titration of those

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## Psychostimulants-Sprinkle forms

- Methylphenidate
  - Focalin XR, Ritalin LA, Metadate CD (NOT Concerta)
- Amphetamine
  - Adderall XR
- Sprinkled on applesauce (also yogurt, ice cream, etc)



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## Nonstimulants

- Atomoxetine/strattera
- Alpha Agonists
  - Clonidine/Catapres.
  - Guanfacine/Tenex
  - Guanfacine/Intuniv
- Modafinil (Provigil)

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## Atomoxetine/strattera

- Not a stimulant
  - Block the reuptake of norepinephrine
  - Ultimately impacts of dopamine
  - Not a controlled substance
    - Easier to manage
- Effect is sustained throughout the day
  - Takes time to “build up” for effect
  - Possible benefits within 2 weeks but full trial usually takes 8 weeks

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## Atomoxetine/strattera

- Dosing is very important
  - “window” of effect
  - Generally once a day but some (often younger) require 2 x dosing
- Generally lower rate of side effects as compared to stimulants
  - Less risk for anxiety, appetite suppression, sleep disturbance, tics
    - Better tolerated in ASP?
  - Can improve enuresis

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## Alpha Agonists

- Can be used alone or in combination with stimulants
  - Often useful in young/medication sensitive patients
- Useful for hyperactivity, insomnia, symptoms of aggression, lability/ irritability, impulsivity, anxiety and tics
  - Do not trigger anxiety as some stimulants can
- Side effects: dry mouth, drowsiness, cognitive dulling, lower BP
  - Side effect profile often cleaner as compared to stimulants

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## Alpha Agonists

- Clonidine (Catapres)
  - (0.1 - 0.3 mg/day)
  - Patch form
- Guanfacine (Tenex)
  - (1 - 3 mg/day)
- Dosage: Typically start with evening doses and titrate toward the morning

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## Clonidine (Catapres)

- Reduces a sympathetic discharge and lowers level of catecholamine production
- Studies reveal improved attention, hyperactivity and impulsivity in children with ADHD
- Smaller studies in ASD improved parent/teacher ratings of hyperactivity, irritability and oppositional behavior
- Side effects include sedation and hypotension

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## Guanfacine (Tenex)

- Similar impact on sympathetic discharge and catecholamine production
  - More selective pharmacological impacts
    - May selectively target prefrontal cortex
    - Greater positive impact on attention
- Studies in a SD reveal positive impact on parent/teacher ratings of inattention and hyperactivity
- Often better tolerated as compared to clonidine but less sedation which can be useful for sleep

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## Intuniv

- Long acting form of guanfacine
  - Guanfacine/Tenex typically dosed 2x - 3x /day
  - This form allows once a day dosing
- Sedation can be problematic in some

PK Parameters in Adults

Parameter	INTUNIV	Guanfacine
	1 mg qd (n = 52)	1 mg qd (n = 12)
C <sub>max</sub> (ng/mL)	1.0 ± 0.3	2.5 ± 0.6
T <sub>max</sub> (h)	6.0 (4.0 - 8.0)	3.0 (1.5 - 4.0)
AUC <sub>0-∞</sub> (ng.h/mL)	32 ± 9	56 ± 15
T <sub>1/2</sub> (h)	18 ± 4	16 ± 3
Relative bioavailability	58	100

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## Nonstimulants

### • Modafinil (Provigil) Armodafinil (Nuvigil)

- Not a stimulant
  - Affects histamine and possibly dopamine (much less as compared to stimulants)
  - Promotes alertness > concentration
- Not approved by FDA in children
  - Approved for narcolepsy, shift phase work
  - Studies demonstrated effect at 400mg in ADHD
  - "safety" concerns regarding rash prevented approval
  - Cost limits use for many

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## Alternative/New Medications

- Omega 3 Fatty Acids
- Memory/Dementia Medications
  - Aricept (donepezil)
  - Exelon (rivastigmine)
  - Namenda (memantine)
- Nicotine analogues

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## Alternative/New Medications

- Omega 3 Fatty Acids
  - Support the neuronal support cells (glia)
  - Work well adjunctively
    - Probably not sufficient for most by themselves
  - Have mood/anti-anxiety properties
  - Also affect attention, memory, language (?)
- Very few side effects
  - GI upset can happen
  - Activation especially if FH of Mood D/O
- Dosing still to be determined

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## Alternative/New Medications

- Memory/Dementia Medications
  - Aricept (donepezil)
  - Exelon (rivastigmine)
- Namenda (memantine)
- Small number of studies (mostly for Aricept)
  - Namenda also studies for Autism
- Helpful when other medications not tolerated

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## Alternative/New Medications

- Amantadine
- Naltrexone

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## Amantadine

- Noncompetitive N-methyl-D-aspartate (NMDA) antagonist
- Indicated for the treatment of Parkinson's
- Some studies indicate benefit for behavioral symptoms in ASD
  - Benefit on clinician rated measures of hyperactivity, but not parent
- Most common side effects include insomnia and somnolence

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**Naltrexone**

- Opiate antagonist
  - Generally used to block the effects of opiates in the body (i.e overdose)
- Open label studies in ASD demonstrate impact on hyperactivity and attention, but results are mixed
- Generally well tolerated, but liver function in times need to be tracked over time

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**New directions?**

- Combination agents
  - Psychostimulant +?
- Cholinergic agonists
  - In development
  - Likely to be indicated for both memory, and ADHD

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**Thank you**

**Support**

- Speaker Bureau
  - Astra Zeneca (Seroquel)
  - Bristol Meyers Squibb (Abilify) (past)
  - Glaxo Smith Kline (Vyvanse)
  - Janssen (Risperidone) (past)
  - Lilly (Strattera)
  - Novartis (Focalin XR/Ritalin LA/Focalin)
  - Pfizer (Zoloft/Geodon) (past)
  - Shire (Vyvanse/Intuniv)
- Research Projects
  - Bristol Meyers Squibb (Abilify) (past)
    - Early Onset Schizophrenia Study (Asarnow, Caplan)

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