

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

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)*

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

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)

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

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.

Medication options

Psychostimulants

History of the drugs

Pharmacology of the drugs

New agents

Nonstimulants

Other drugs

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

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)

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"

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. ^{1,2}

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

Reuptake Block Effects ADHD Symptoms

Amplification of dopamine (DA) may improve performance in patients by decreasing distractibility or facilitating interest in the task.¹

Increasing postsynaptic norepinephrine (NE) may improve attention, alertness, vigilance, and executive function.²

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

Dopamine Neurotransmission-ADHD

Dopamine

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

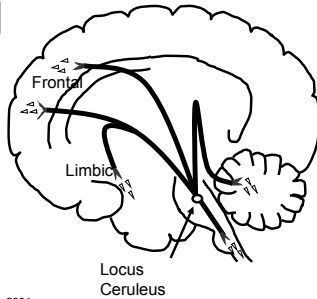


Solanto. *Stimulant Drugs and ADHD*. Oxford; 2001

Norepinephrine Neurotransmission- ADHD

Norepinephrine

- Dampens noise
- Executive operations
- Increases inhibition



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

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.

Stimulant side effects

Limit dose efficacy

Appetite decrease
Weight loss.
Insomnia

Transient/dose increase

GI issues
Headache

Possible over time

Nervousness/anxiety.
Irritability.
Dysphoria

Variable

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

Methylphenidates

Short acting

Ritalin	2-4 hrs
Focalin [®]	3-5 hrs

Long acting

Metadate [®] CD	6-8 hrs
Ritalin [®] LA	8-9 hrs
Focalin [®] XR	10-12 hrs
Concerta [®]	10-12 hrs
Daytrana [®] (patch)	12+hrs

Amphetamines	
Short Acting	
Dextroamphetamine	
Dexedrine/Dexrostat	5-6 hrs
Mixed Salts	
Adderrall [®]	6 hrs
Long Acting	
Mixed Salts	
Adderrall XR [™]	8 hrs
Dextroamphetamine	
Dexedrine Spansules	6-8hrs
Vyvanse	12 hrs

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	

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

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

Medication considerations
<p>These various options differ in amount and time of medication release</p> <ul style="list-style-type: none"> Can impact the timing and intensity of "rebound" <p>Choice depends on individual needs of the patient</p> <ul style="list-style-type: none"> Sensitivity to specific side effects Time in which greater symptom coverage is needed <p>Longer acting agents are generally preferable.</p> <ul style="list-style-type: none"> More practical for patient/parent. No need to get second dose, including at school

Medication considerations
<p>Daytrana transdermal patch</p> <ul style="list-style-type: none"> Useful for those individuals who cannot swallow. Tactile/sensory issues may limit use in ASD Can control time of onset and offset <p>Associated side effects.</p> <ul style="list-style-type: none"> Anxiety/mood symptoms, sometimes more common with certain agents <p>Sprinkle forms</p> <ul style="list-style-type: none"> Useful for those individuals who cannot swallow Also allow more accurate titration of those

Psychostimulants-Sprinkle forms

Methylphenidate

Focalin XR, Ritalin LA, Metadate CD (NOT Concerta)

Amphetamine

Adderall XR

Sprinkled on applesauce (also yogurt, ice cream, etc)



Nonstimulants

Atomoxetine/strattera

Alpha Agonists

Clonidine/Catapres.

Guanfacine/Tenex

Guanfacine/Intuniv

Modafinil (Provigil)

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

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

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

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

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

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

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 _{max} (ng/mL)	1.0 ± 0.3	2.5 ± 0.6
T _{max} (h)	6.0 (4.0 - 8.0)	3.0 (1.5 - 4.0)
AUC _{0-∞} (ng.h/mL)	32 ± 9	56 ± 15
T _{1/2} (h)	18 ± 4	16 ± 3
Relative bioavailability	58	100

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

Alternative/New Medications

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

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

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

Alternative/New Medications

- Amantadine
- Naltrexone

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

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

New directions?

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

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)
