

ADHD Treatment: Side Effects and Management

Derek Ott, M.D., M.S.
Assistant Clinical Professor of Psychiatry
Division of Child Psychiatry
David Geffen School of Medicine at UCLA
Director, Pediatric Neuropsychiatry Clinic
Private Practice, Los Angeles, CA

Medication options

- Psychostimulants
 - Methylphenidates
 - dexamethylphenidate
 - Amphetamines
 - dextroamphetamine
- Nonstimulants
 - Atomoxetine
 - Guanfacine/Intuniv
 - Clonidine/Kapvay

Safety of Stimulants

- Despite descriptions in the lay press, stimulants are very safe and effective.
 - Efficacy and safety of stimulants established in numerous studies in children, adolescents and adults with ADHD
 - Greater rate of side effects in very young (i.e. preschool)
- Most individuals tolerate these medications very well
- The most widely studied and documented areas in psychiatry

Stimulant side effects

Transient/dose increase

- GI issues
- Headache

Limit efficacy

- Weight loss
- Insomnia
- Change of "personality"
- Activation

Variable

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

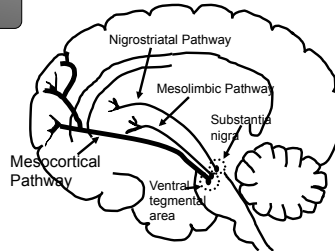
Emergent

- Anxiety/nervousness
- Irritability
- Dysphoria
- Suicidality
- Psychosis
- Tics

Dopamine Neurotransmission-ADHD

Dopamine

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

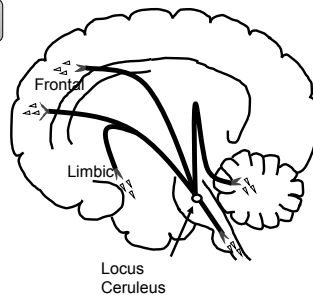


Solanto. Stimulant Drugs and ADHD. Oxford; 2001.

Norepinephrine Neurotransmission- ADHD

Norepinephrine

- Dampens noise
- Executive operations
- Increases inhibition



Solanto. Stimulant Drugs and ADHD. Oxford; 2001.

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/Dextrostat 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
 - Adderall XR
- Transdermal patch
 - Daytrana
- Prodrug
 - Vyvanse

Newer ADHD Medications	
Concerta®:	methylphenidate formulated to mimic T1D duration (12 hours)
Adderall 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)

Stimulant side effects	
Transient/dose increase	Variable
<ul style="list-style-type: none"> • GI issues • Headache 	<ul style="list-style-type: none"> • "Rebound" • Return of prior symptoms often to slightly higher level
Limit efficacy	Emergent
<ul style="list-style-type: none"> • Weight loss • Insomnia • Change of "personality" • Activation 	<ul style="list-style-type: none"> • Anxiety/nervousness • Irritability • Dysphoria • Suicidality • Psychosis • Tics

Transient side effects

- Headache
- GI issues
 - Abdominal pain
 - Nausea
 - Dry mouth

Headache

- Typically transient/early in treatment
- Treatment
 - Often responds to rehydration
 - Over-the-counter pain medication.
- Migraine-rare

GI Issues-Nausea

- Usually at initiation or following dose increase.
 - Often will fade with time.
- Sometimes occurs with certain medications but not others
- Reduced in the presence of food
- Chocolate especially dark chocolate can also be beneficial

GI Issues-Abdominal Pain

- Fairly rare
- Usually at initiation or following dose increase.
- May occur with some drugs preferentially but not others
- May depend on meal status

- Can lead to discontinuation

- *In the presence of strattera, consider further evaluation given possible rare hepatic effects of this drug*

GI Issues-dry mouth

- Often early in treatment.
- More often in adults especially at higher doses.

- Drinking water usually does not work.
- Sugarless mints are useful.
- Other products (i.e. Biotene) can also be helpful

-

Psychostimulants-Sprinkle forms

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



Rebound

- Return of prior symptoms often to a higher level after medication affect wears off
 - Often manifested by restlessness (including self stimulatory behavior), impulsivity, hyperactivity, mood changes
- Some people impacted more than others
 - Underlying mood disorder?
- Impact of various drugs
 - Short versus long acting stimulant
 - Mechanism of release/termination of effect
 - Duration of action

Rebound

- Relevant factors
 - Time when medication wears off
 - Late afternoon versus evening
 - Circadian rhythms
 - Sleep status/level of fatigue
 - Calories
 - Time of last meal/blood glucose
 - Overall caloric intake
 - Emotional
 - Comorbid mood disorder, anxiety
 - Other factors-family, environmental, house hold transitions

Rebound

- Examination of calories consumed.
- Regular snacking often with higher caloric items.
- Additional medication/supplementation
 - Chocolate
 - Caffeine
 - 5-HTP
 - Short acting stimulants
 - Alpha-2 agonists (guanfacine/Intuniv)
 - Atypical antipsychotics

Confounding side effects

- Insomnia
- Appetite suppression
- Weight loss
- Change of “personality”
- *Limited ability to achieve efficacy*

Confounding -insomnia

- Regular and good sleep needed for full benefit of medication
- High rate of sleep disturbance in ADHD in general
 - Exist even prior to use of medications
 - Early-morning awakenings often present
 - Sleep apnea
- Need to characterize nature of sleep disturbance
- Generally early insomnia

Confounding -insomnia

- Triggered by
 - Activation from the stimulant present later in the day
 - Some people more susceptible than others
 - “Rebound”
 - Creates difficulties settling into bed and falling asleep
- *Note some patients benefit from late dose or even bedtime dose of medication*

Confounding -insomnia

- Solutions
 - Adjust timing of morning medication
 - Give dose earlier in the day if possible
 - Food and appetite issues possible limiting factors
 - Sometimes patient awake for medication administration
 - Daytrana patch can be applied while asleep
- Selection of alternative agent with shorter duration
 - Vyvanse >Adderall XR >Adderall/Dexedrine
 - Concerta >Focalin XR >Ritalin LA>Metadate CD >Ritalin

Confounding -insomnia

- Solutions-continued
 - Addition of supplements.
 - Melatonin
 - Tryptophan
 - Valerian root
 - Addition of medication
 - Diphenhydramine/Benadryl
 - Clonidine/Catapres
 - Deseyrel/Trazodone
 - Mirtazapine/Remeron.
 - Atypical antipsychotic-risperidone,olanzapine,quetiapine, etc

Appetite suppression

- Very common side effect
 - Less common in adults
 - Often more with amphetamine products
- Tolerance may develop to this over time
- May impact
 - Weight loss
 - “rebound”
 - Focus (brain needs fuel to function)
- May can be related to nausea or other GI effects

Appetite suppression

- If related to nausea or other GI effects address this
 - Chocolate and other remedies for nausea
 - Medication after meals
- Medication adjustment
 - Not using medication or use of partial dose during the weekends or other times.
 - “medication holidays” no longer the norm
- Daytrana patch

Daytrana transdermal patch

- Benefits
 - Because bypasses G.I. tract have lower GI side effects
 - Useful for those individuals who cannot swallow.
 - Can control time of onset and offset
- Limitations
 - Rash/sensitivity
 - Hydration with lotion is critical
 - Tactile/sensory issues may limit use in ASD

Weight loss

- Caution
 - Premorbidly underweight
 - Younger (i.e preschool)
 - Selective/”picky” eaters
 - ASD
 - Adolescent females
- Monitoring
 - Weight, growth chart
 - Coordination with pediatrician and others

Weight loss>Growth

- Concerns as to the effect of stimulants on growth have existed for many years
- Related to known anorexic effects, and that dopamine inhibits growth hormone
- Despite numerous studies examining effects of stimulants on growth, a clear consensus has yet to be established

Weight loss>Growth

- ADHD is a developmental condition which affects development in other spheres (emotional, social, academic, *physical*)
 - Delayed puberty more common
 - Stimulated related growth deficits related to early temporary manifestation of ADHD
- Older studies suggested greater impact of stimulants on growth/height
- Basis for recommendation of “drug holidays”
 - Not giving medication during weekends, vacations or summer

Weight loss>Growth

- Longitudinal MTA study revealed impact on the rate of growth
- Some groups affected more
 - Greatest for taller + heavier children
 - Greater for children versus adolescence
 - Higher dose stimulants
- Newer studies suggest growth deficits attenuate over time with NO ultimate impact on overall final height

Weight loss

- Maximize calories throughout the day
 - Eating breakfast prior to medication administration
 - Calorie loading in AM
 - Protein shakes
 - Preferred food items (i.e pizza, cheeseburgers, etc)
 - Eating later in PM after medication effect wears off
 - Eating remainder of dinner later
 - “Second dinner”
 - Consistent/frequent snacking
 - May need prompts/reminders as not hungry
 - Portable snacks (i.e bars, trail mix, nuts, etc) often beneficial

Weight loss

- Supplemental medications.
 - Usually considered after other options are exhausted.
 - Cyproheptadine/Periactin
 - Hydroxyzine/Atarax
 - Mirtazapine/Remeron.
 - Atypical antipsychotic-olanzapine/Zyprexa quetiapine/Seroquel, risperidone/Risperdal
 - May also provide other relevant benefits (i.e. sedation for sleep, anxiety reduction, mood affects)

“Change of personality”

- Can happen be dose-dependent (i.e. higher doses)
- Preferentially with certain medications?
- Differential
 - Appropriate treatment of ADHD symptoms (i.e.no longer class clown or jokester)
 - Truly more subdued or even lethargic
 - Depression?
- All of the above possibilities need to be discussed with patient and family

“Change of personality”

- Solution
 - Further psychoeducation about treatment
 - Reduction of dose, if possible.
 - May require supplementation with other medication
 - Change medication, if possible.

Emergent side effects

- Anxiety
- Irritability
- Dysphoria
- Suicidality
- Psychosis
- Tics

Anxiety

- Comorbid anxiety very common in ADHD
- Treatment with stimulants can reduce anxiety
 - Performance anxiety (academic).
 - Social anxiety
 - “Too many thoughts before bed”
 - Need for compulsive tendencies (list making)
- Treatment with stimulants can increase anxiety
 - Activation
 - Obsessionality/compulsions
 - Behaviors/habits-skin picking, hair pulling

Anxiety

- Education about benefits of medication
- Change of medication
 - Amphetamine > methylphenidate
- Dose adjustment
- Selective use of medication
 - Not using during stressful situations
- Addition of another medication.

Anxiety

- Addition of anti-anxiety medication when
 - Anxiety is overwhelming.
 - Anxiety is interfering with attention.
 - OCD/symptoms are interfering
- Choices
 - SSRI's
 - Buspirone/BuSpar
 - NOT benzodiazepines (Xanax, Ativan) in younger

Irritability

- Need to separate from untreated ADHD symptoms
- Can be related to "rebound"
 - Can even occur in the morning sometimes
- Solution
 - If untreated ADHD treat ADHD.
 - If rebound treat the rebound
 - Rule out depression or anxiety
 - Change of medication.
 - Amphetamine > methylphenidate?

Dysphoria

- When does that occur?
 - Throughout the day
 - In the morning? (irritability)
 - “Rebound?”
 - Emerge over time
 - Episodic or consistent
- Prior or family history of depression?
- Relationship with food/sleep

Dysphoria

- Change of medication.
 - Amphetamines > methylphenidate
 - Atomoxetine/strattera
- Add supplements/medication
 - Omega-3 fatty acids
 - 5HTP
 - SSRI?
 - Suicide concerns

Suicidality

- Not a specific concern with stimulants per se.
- Can occur during rebound or more severe “crash” which occurs with some medication especially with high doses
- Important to distinguish if episodic or more consistent.
- Atomoxetine/Strattera
 - Higher rates versus placebo (0.4% versus 0.1%)

Psychosis

- Misperception/misinterpretation vs distortion vs delusions/paranoia
- Rare but can occur especially if vulnerable
 - Poor reality testing at baseline
 - Autistic spectrum disorder
 - Learning disorder
- More common with certain medications?
- Usually resolves with discontinuation or dose reduction
 - Rarely requires separate treatment

Tics

- Tics=rapid repetitive movements experienced as outside of volitional control
- Differential
 - Habits> Compulsions
 - Biting of nails
 - Hair twirling
 - lip licking/stretching of mouth over braces
 - Stereotypical behaviors
 - More often associated with autistic spectrum disorders.
 - May also occur in individuals with similar neurologic disorders

Tics

- Differential -continued
 - Stereotypical behaviors
 - More often associated with autistic spectrum disorders.
 - May also occur in individuals with similar neurologic disorders
 - Other abnormal movements
 - Dyskinesia (i.e. associated with use of atypical antipsychotics)

Clinical possibilities

- ADHD with no evidence of tics
- ADHD with family history of tics
-
- ADHD with prior stimulant related tics
- ADHD with Tic disorders +Tourette' s

Clinical observations

- Some ADHD children develop tics with first exposure to low-dose stimulants
 - >Transient, disappear when discontinued, persistent
- Some children with stimulant response of ADHD appear to develop "tolerance" with tics emerging with dose increases + higher doses
 - >transient, wane what time, persistent
- Some with early stimulant induced tics fade over time
 - Subsequent re-challenge no further tics
- Some children with severe tic disorders may improve with stimulants, or even worsen when stimulants or discontinued

Tics

- New onset versus worsening
- If develop typically wait and monitor
 - Most common tic disorder in younger is transient tic disorder, especially in boys (peak incident 6-8 years)
 - Tics may come and go independently of medication and other factors
 - May fade with time especially if occur after dose increase
- May consider slight lowering of does if possible

Tics

- Consider
 - Form of methylphenidate (lower risk overall?)
 - Non-stimulant (Strattera, Intuniv)
 - Additional medication to treat tics
 - SRI's, guanfacine/Tenex/Intuniv, clonidine/Catapres/Kapvay
 - Atypical antipsychotics

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/Fanapt)
 - Pfizer (Zolofit/Geodon) (past)
 - Shionogi (Kapvay)
 - Shire (Vyvanse/Intuniv)
- Research Projects
 - Bristol Meyers Squibb (Abilify) (past)
 - Early Onset Schizophrenia Study (Asarnow, Caplan)
