Antidepressants in the Pediatric Population

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Disclosure

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Learning Objectives:

• Identify evidence-based pharmacologic treatments for pediatric depression, pediatric bipolar disorder, and pediatric ADHD.

• Make treatment recommendations for children and adolescents
Criteria for Major Depressive Episode: DSM-5

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is (1) depressed mood or (2) loss of interest or pleasure.
- Note: Do not include symptoms that are simply a feature of a general medical condition, or normal reactions to significant life stressors.
- Depressed mood most of the day, nearly every day, as indicated by either subjectively reported mood, or observation made by others (e.g., definite melancholia); Note: In children, dysphoria, or irritability.
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective report, or observation made by others).
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5 percent of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gain.
- Fatigue or loss of energy nearly every day.

Criteria for Major Depressive Episode: DSM-5

- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional)
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation
- Without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

Risks of Untreated Depression

- Adverse effects on development of emotional, cognitive, and social skills
- Suicide attempts and completion
- Substance abuse
- Legal problems
- Early pregnancy
- Poor work, academic, and psychosocial functioning
Treatment

- Treatment should include education, supportive management for the family and patient, and school involvement
- Mild depression with limited psychosocial impairment (absent suicidality or psychosis) may be treated with education, support, and case management related to stressors
- If no response in 4-6 weeks, may need to consider therapy and/or medication.

Treatment warranting more specific therapies and/or antidepressants

- Chronic & recurrent depression
- Moderate to severe psychosocial impairment
- Comorbid disorder(s)
- Strong family history of depression

Antidepressants

- Pharmacologic approach is based on a few randomized controlled pediatric trials, data available from adult studies, and anecdotal clinical and research experience
**Tricyclic Antidepressants (TCAs)**

- Amitryptiline, clomipramine, desipramine, doxepin, imipramine, nortryptyline
- No evidence of superiority vs placebo for any of them
- Can have significant side effects (anticholinergic, QT prolongation)
- Cardiotoxic in OD
- To be avoided in children and adolescents

**Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)**

- Venlafaxine desvenlafaxine, duloxetine,
- One study showed that venlafaxine is as effective as SSRIs in patients with treatment-resistant depression but has a worse side-effect profile (Brent et al 2008)
- No consistent evidence about the others

**Other Antidepressants**

- Buspirone, nefazodone, trazodone
- Evidence of efficacy is lacking in this age-group
The safest and most commonly used antidepressants in children & adolescents.

- RCT's using fluoxetine, sertraline, escitalopram, and paroxetine have shown that children and adolescents with MDD responded significantly better to acute treatment with these antidepressants (50%-60%) than with placebo (30%-50%) (Bridge et al. 2009).

**SSRIs**

**Selective Serotonin Reuptake Inhibitors**

- Has shown the most consistent data with separation from placebo in RCTs.
- First SSRI to be approved for child & adolescent MDD (ages 8-18 yo)
- 10-40 mg/day
  

**Fluoxetine**

- FDA approved to treat MDD in adolescents (ages 12-17 yo)
- 10-20 mg escitalopram > placebo
  
Other SSRIs

• For sertraline and citalopram, there is less evidence of effectiveness.
• May be effective in patients that did not respond to Fluoxetine or Escitalopram.

How to choose an antidepressant?

• Choose by efficacy and safety
• Any adverse effects and response vs non-response in a previous episode should be considered
• SSRIs first line medication for MDD in pediatric population
• Examples: Fluoxetine (prozac), Escitalopram (lexapro), Sertraline (zoloft), Citalopram (celexa)

FDA Review

• An FDA sponsored meta-analysis, conducted in collaboration with Columbia University (Hammad et al. 2006)
• 26 RCTs ranging from 4-16 weeks:
  • 16 in MDD
  • 4 in OCD
  • 3 in GAD
  • 1 in social anxiety disorder
  • 1 in ADHD
• 9 meds included in this review (Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram, Bupropion, Venlafaxine, nefazadone, and Mirtazapine)
Pooled analyses of these studies found an excess of SI and attempts noted in children and adolescents taking antidepressants (roughly 4% in those taking medication vs. 2% in those taking placebo)

No suicides occurred in these trials

FDA could not rule out an increased risk for suicidality in any of these medications

Blackbox warning applies to all antidepressants

Dosages prescribed for children and adolescents are similar to those used for adults

Start low and go slow; gradually titrate upwards

Treat with adequate doses for at least 4-6 weeks

Assess at 4-6 week intervals

Carefully monitor for emergent spontaneous suicidality

See patients every week for the first four weeks

Every 2 weeks for the next 4 weeks

After 12 weeks of taking antidepressant, follow healthcare provider’s advice about how often to come back.
Conclusion for now:

- Spontaneous reported suicide adverse effects appear to be more common with antidepressants than placebo.
- However, the risk-benefit ratio seems to be favorable, with careful monitoring.
- Need more studies to clarify if risk-benefit is less favorable for children vs adolescents.

Risk Factors for increased SAEs?

- Gender
- History of suicidality
- Fit of suicidality
- Disorder Type
- Severity of depressive cognitions at intake
- Dosages
- Medication half-life
- Type of antidepressant
- Treatment Duration
- Compliance vs Noncompliance with treatment
- Induction of agitation, activation, or hypomania
- Susceptibility to SEs

Pharmacokinetics

- Fluoxetine – half-life of 24-72 hours in children
- Half-lives of most SSRIs between 14-16 hours
- Some studies have suggested that some SSRIs may need bid dosing
- More pharmacokinetic studies needed on other antidepressants. Children and adolescents may metabolize these meds faster than adults.
Interactions with other medications

- Most of the current SSRIs used are metabolized by CYP3A4 and/or CYP2D6 enzymes.
- Watch out for toxicity due to inhibition of these enzymes.
- CAUTION:
  - Neuroleptics
  - TCAs
  - Atypical antipsychotics
  - Warfarin
  - Antiarrhythmics
  - Antihypertensives
  - Theophylline
  - Antidepressants
  - carbamazepine

Discontinuation

- Abrupt cessation of antidepressants may cause withdrawal effects (fatigue, irritability)
- May look like recurrence of depression.
- Taper down slowly with monitoring by prescribing physician
- Duration of treatment should be for at least 6 months after recovery

TREATMENT- RESISTANT DEPRESSION

- Birmaher and colleagues (2009) defined treatment resistance as a youth who symptoms of depression and functional impairment persist after 8-12 weeks of optimal pharmacological treatment or 8-16 session of IPT or CBT
- A partial response to treatment in MDD found in 60% youth
- 20-30% may not respond at all (Birmaher et al 2005; Brent et al. 2009, Emslie et al. 2008; March et al. 2004)
- Chronic depression in children usually does not remit spontaneously and is not responsive to placebo (Practice Guidelines 2009)
WHY are they not responding?

- Wrong Diagnosis
- Inadequate Trial
- Inadequate Dosage
- Noncompliance
- Comorbidity
- Presence of BPMD (Brent et al. 1998, 2009; Hughes et al. 1999; Practice Guideline 2000)
- Substance Abuse
- Internal Depression
- Rajenxious/ongoing conflicts
- Bullying/stressors/ongoing conflicts
- Dysfunctional/school/neighborhood
- Cultural/Ethnic Issues
- Side Effects of medication
- Other Medications (i.e., steroids)
- Exposure to negative events

Treatment of SSRI-Resistant Depression in Adolescents Study (TORDIA)

- Is the only RCT of adolescents with treatment-refractory depression (Brent et al. 2008).
- This study had a large number of adolescents with MDD
- Study showed that combination of CBT + antidepressant had greater efficacy than antidepressant alone (54.8% vs 40.5%)

TORDIA

- There were no differences between the medications used (fluoxetine, citalopram, & venlaxafine).
- Follow up showed remission with about 60% remission at 72 weeks
- 25% of the remitted patients relapsed later (Emslie et al. 2010; Wood et al. 2011)
1.) Optimize Initial Treatments
   • A. Extend the initial medication trial
   • B. Increase the dosage
2.) Switch strategies
3.) Augment or combine strategies

COMORBIDITIES

- ADHD
- Anxiety Disorders
- OCD
- Conduct Disorder
- Eating Disorders
- PTSD
- Substance Abuse

CONTINUATION THERAPY

- Rate of MDD relapse is high
- Continue treatment for 6-12 months after complete symptom remission
- Teach patient and family early signs of relapse
- Maintain medication dose used for remission of symptoms
MAINTENANCE THERAPY

- Main goal: Prevent Recurrences
- Usually lasts from 1 year and beyond

References


Psychopharmacology in Pediatric Bipolar Disorder

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DSM-V Criteria for Manic Episode

- First, the individual has a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 week (or any duration if hospitalization is necessary).
- Second, during the period of mood disturbance, 3 or more of the following symptoms persisted (if the mood is only irritable) and have been present to a significant degree:
  - Inflated self-esteem to levels of grandiosity
  - Decreased need for sleep
  - More talkativeness than usual, often characterized by pressured speech with a sense of a need to keep talking
  - Flight of ideas or a subjective feeling that thoughts are racing
  - Distractibility
  - Increased goal-directed activity or psychomotor agitation
  - Excessive involvement in pleasurable activity that has a high potential for painful consequences (e.g., hypersexuality, excessive spending, impulsive travel)

- Third, the symptoms do not meet the criteria for a mixed episode.
- Fourth, the mood disturbance is severe enough to cause marked social impairment in occupational functioning, social activities, or relationships with others. Hospitalization may be necessary to prevent harm to self or others or if psychotic features are present.
- Fifth, the symptoms are not due to the direct physiologic effects of a substance or a general medical condition.

Hypomanic Episodes

- Elevated, expansive, or irritable mood lasting for at least 4 consecutive days
- At least 3 of the following symptoms are also present:
  - Grandiosity or inflated self-esteem
  - Diminished need for sleep
  - Pressured speech
  - Racing thoughts or flight of ideas
  - Clear evidence of distractibility
  - Increased level of goal-focused activity at home, at work, or sexually
  - Engaging in activities with a high potential for painful consequences
Prognosis

- Early onset BPD has a course usually more severe than that of late-onset BPD
- The course of illness is more refractory to treatment with earlier-onset of BPD
- Increased risk of suicide

Usually start with Lithium, an anticonvulsant, or an atypical antipsychotic for initial treatment of PBD.

- If partial response to monotherapy, may add a medication from a different drug class.
- If no response to a given medication, switch to medication from different drug class.

LITHIUM CARBONATE

- Naturally-occurring salt
- First medication approved by FDA to use in children with mania in PBD (12 yo and older).
- Used in children and adolescents with documented recurrent mania/mixed episodes as prophylaxis of PBD.
- CoLT (Collaborative Lithium Trials) group started testing Li in juvenile mania in 2006.
- There have been some prospective studies that have found Li to be well-tolerated and effective in PBD.
Prior to Initiating Li

- Thorough medical history
- **Li is a known teratogen! Pregnancy test in all females of child-bearing age**
- Baseline Bloodwork
- Electrocardiogram

Dosing of LITHIUM

- Dosing strategies were studied by Findling et al (2011) with Li monotherapy.
- Start 300 mg qd and can be increased by 300 mg q 4-5 days (in divided doses) based on clinical response & serum levels.
- Weight-based dosing can attain therapeutic levels in a shorter time - 15-20 mg/kg/day in divided doses (Weller et al 1986).
- Take serum levels 12 hours after last dose (And q 4-5 days as dose being titrated).
- Screening bloodwork should be repeated once at stable Li dosage.
- Li levels, TSH, and renal function should be evaluated at least q3mths.
- Narrow therapeutic index.
- Therapeutic range 0.6-1.4 mEq/L.

Li Side Effects

- **GI symptoms (stomachache, n/v/d)**
- CNS (slowed mentation, ataxia, tremor)
- Renal (polyuria, polydipsia)
- Dermatologic (acne-like rash, hair loss)
- Endocrine (weight gain, hypothyroidism)
Drug Interactions

- NSAIDS – may increase Li levels
- Thiazide diuretics – may increase Li levels
- Theophylline – may decrease Li levels
- Caffeine – may decrease Li levels
- Sports drinks/salty-snacks (in excess) – may decrease Li levels


CAUTION

- DC Li if fever, n/v/d
- Extreme exercise in hot weather
- Rigorous dieting

ATYPICAL ANTIPSYCHOTICS

- Useful as monotherapy and as an adjunct medication for pediatric patients with BP I Disorder.
- Reduced ability to cause Extrapyramidal side effects (compared to older antipsychotics)
- Reasonably well-tolerated
- Concerns about lipid profile changes, weight gain, glucose intolerance, and still movement disorders (dystonia, parkinsonism, and tardive dyskinesia)
- Concerns, risk/benefits, and short-term/long-term side effects should be discussed thoroughly with patient and guardians
- Avoid using with other sedating medications, other medications that can potentially lengthen the QT interval or interfere with hepatic metabolism of the medication.
Prior to Initiating Atypicals

- Detailed medical history and PE (includes specific history related to endocrine, weight, cardiovascular status, neurological status, movement disorders)
- Abnormal Involuntary Movement Scale
- Bloodwork (CBC w/diff, glucose, lipid profile, LFTs)
- EKG

ARIPIPRAZOLE (Abilify)

- Partial dopamine agonist
- FDA approval for the acute and maintenance treatment of manic & mixed episodes in Bipolar I DO (ages 10-17 years).
- One randomized, double-blind, placebo-controlled study of 296 patients, aged 10-17 yo, showed that dosages of aripiprazole (at dosages of 10 and 30 mg/day), was superior to placebo in the acute treatment of manic and mixed episodes (Findling et al. 2009).

Dosing

- Usually QD dosing
- Initiate at 2- or 5 mg qhs and may increase q2-3 days by 2- or 5 mg
- Maximum approved FDA dose is 30 mg/qd
**Side Effect Profile**
- GI (nausea, emesis)
- CNS (headache, activation, sedation, akathisia)
- General (weight gain)

**OLANZAPINE (Zyprexa)**
- FDA approval for the acute treatment of manic or mixed episodes associated with Bipolar I DO in adolescents (13-17yo).
- Several studies that included a case series, open-label monotherapy trials, and a double-blind, randomized placebo-controlled trial have shown the efficacy of Olz, as well as the greater reduction in manic symptoms vs placebo.

**Dosing**
- Initiate at doses of 2.5 or 5 mg & titrate in these same increments
Side Effect Profile

- Endocrine (Glucose Intolerance)
- CNS (Headache, sedation)
- General (Weight gain)

QUETIAPINE (Seroquel)

- FDA approval for the acute treatment of manic episodes in pediatric patients with BP I DO (10-17 yo)
- A retrospective chart review (Marchand et al. 2004), and 2 randomized, placebo-controlled trials (DelBello et al 2006 and 2007) showed that Quetiapine was more effective in treating acute manic symptoms in PBD vs placebo.

Dosing

- BID dosing
- Initiate at 25 mg bid and titrate by 50-100 mg/day in adolescents or 25-50 mg/day in younger children.
Side Effect Profile

- Cardiovascular (Elevated BP)
- CNS (Sedation, orthostasis)
- Visual (Cataracts)
- General (Weight gain)

RISPERIDONE (Risperdal)

- First atypical antipsychotic to get FDA approval for treatment of acute mania or mixed episodes associated with BP I DO (10-17 yo).
- Comparative studies, prospective open-label studies (Biederman et al. 2005 and 2005c), randomized study of Risperidone vs placebo (Haas et al. 2009) found Risperidone helped with improvement of symptoms, and it was superior to placebo in acute treatment of manic or mixed episodes.

Dosing

- QD or bid dosing Initiate between 0.25 mg/day to 0.5 mg/day and can be titrated by 0.5 to 1 mg/day q 24 hours, as tolerated.
- No additional benefit seen above 2.5 to 4 mg/day for bipolar mania in studies.
Side Effect Profile

- CNS (sedation, headache)
- Endocrine (Glucose intolerance, prolactin elevation)
- General (Weight gain)

ASENAPINE (Saphris)

- Very recently (March 13, 2015) received FDA approval for acute treatment of manic or mixed episodes associated with BP I DO (10-17 yo)
- First atypical antipsychotic to be approved for pediatric Bipolar DO in the last 5 years.
- Approval based on results of a 3-week monotherapy trial with 403 pediatric patients (10-17 yo) of whom 302 patients received Asenapine bid in 2.5/5 or 10 mg/qd dosages. This study showed improvement in the Young Mania Rating Scale total score and Clinical Global Impression Bipolar Severity of illness overall score vs. placebo

Dosing

- A sublingual formulation
- BID dosing
- 2.5mg, 5 mg, and 10 mg tabs
Side Effect Profile
- CNS (sedation, dizziness, numbing of the mouth)
- GI (nausea)
- General (weight gain, increased appetite)

ANTICONVULSANTS
- Divalproex Sodium (Depakote)
- Lamotrigine (Lamictal)
- Carbamazepine (Tegretol)

- These have approval for use in BPD in adults
- No FDA approval for use in PBD
Divalproex Sodium (Depakote)

- FDA approval for treatment of mania in adults (since 1994) – but not for children and adolescents
- More frequently prescribed to children and adolescents, with PBD, than other anticonvulsants.
- The longer-term use of this med in PBD has been evaluated in 2 published studies:
  - Pavuluri et al (2005) showed that children (5-18 yo) achieved response rate of 73.3% and remission rate of 52.9% during study.
  - Findling et al (2005) did 18mth, double-blind, maintenance comparison of Li and VPA in 5-18 yo with BPD. Li and VPA had comparable efficacy for maintenance therapy.

Divalproex Sodium (Depakote)

- Monotherapy has not been found to be sufficient as maintenance therapy for PBD (Findling 2005)
- For mixed or manic episodes in PBD, a randomized-controlled trial did not find Divalproex to be superior to placebo in youth (10-17 yo) (Wagner et al 2009).

- Dulcan M, Lake MB: Child & Adolescent Psychiatry 4e,301-304,2012

Pediatric Bipolar Depression

- More studies needed evaluating treatment for PBD.
- Limited studies which have researched Li, Lamotrigine, and Quetiapine
What if Monotherapy is not enough?

- Partial Responders
- Psychosis

Combination Pharmacotherapy

- Li + VPA has shown efficacy in PBD (Findling et al 2003)
- Li + antipsychotics effective (Kafantaris et al 2001)
- VPA + Quetiapine effective for adolescent mania (DelBello et al 2002)
- Li or VPA + Risperidone has shown efficacy in pediatric mania (Pavuluri et al 2004)

References

ADHD and Treatment with Medications

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DSM V Criteria For ADHD

I. Either A or B:
   Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is inappropriate for developmental level.
   Inattention
   - Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
   - Often has trouble keeping attention on tasks or play activities.
   - Often does not seem to listen when spoken to directly.
   - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
   - Often has trouble organizing activities.
   - Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
   - Often loses things needed for tasks and activities (e.g. toys, school assignments, pencils, books, or tools).
   - Is often easily distracted.
   - Is often forgetful in daily activities.
Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:

- Hyperactivity
  - Often fidgets with hands or feet or squirms in seat when sitting still is expected.
  - Often gets up from seat when remaining in seat is expected.
  - Often excessively runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
  - Often has trouble playing or doing leisure activities quietly.
  - Is often "on the go" or often acts as if "driven by a motor": adults will often feel inside that they were being driven by a motor.
  - Often talks excessively.

- Impulsivity
  - Often blurts out answers before questions have been finished.
  - Often has trouble waiting one's turn.
  - Often interrupts or intrudes on others (e.g., butts into conversations or games).

II. Several symptoms that cause impairment were present before age 12 years.

III. Several impairment from the symptoms is present in two or more settings (e.g., at school/work and at home).

IV. There must be clear evidence that the symptoms interfere with, or reduce the quality of social, academic, or occupational functioning.

V. The symptoms do not happen only during the course of Schizophrenia, or other Psychotic Disorder. The symptoms are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).
• Based on these criteria, three types of ADHD are identified:
  • IA. ADHD, Combined Presentation: if both criteria IA and IB are met for the past 6 months
  • IB. ADHD, Predominantly Inattentive Presentation: if criterion IA is met but criterion IB is not met for the past six months
  • IC. ADHD, Predominantly Hyperactive-Impulsive Presentation: if Criterion IB is met but Criterion IA is not met for the past six months.


• For individuals 17 yo and above, only 5 or more symptoms are needed.


HALLMARK SYMPTOMS
  • Inattention
  • Hyperactivity
  • Impulsivity
Neurochemical Factors

- Dopamine
- Norepinephrine

No single theory that explains the psychostimulant mechanism on the CNS that decreases the symptoms of ADHD.

- Theory is that psychostimulants release catecholamines & block their reuptake.
- Neurobiological studies have shown that dysregulation & alterations of mostly dopaminergic & noradrenergic systems in the brain stem, striatum, cerebellum, and frontocortical areas are involved in ADHD (Willens et al. J Clinical Psychiatry 2006:67(suppl 8)).

Evaluation for ADHD

- History from multiple informants: Child, parents, teachers
- Age of onset
- Impairments seen in minimum of 2 settings
- 6/9 symptoms in either or both inattentive and Hyperactivity-Impulsivity symptom lists
- 6 month duration of symptoms
- Differential diagnosis
PSYCHOSTIMULANTS

- The first line of medication treatment for ADHD
- Stimulant medications are the most commonly used for this disorder
- Non-stimulants are also used
- DO NOT CURE ADHD
- Individually-based
- Patient must be monitored on a regular basis by doctor

Controversy in Use of Psychostimulants

- Related to their classification as a controlled substance (Drugs of abuse)
- Council on Scientific Affairs, of the AMA, concluded that the "risk-benefit ratio of stimulant treatment in ADHD must be evaluated and monitored on an ongoing basis in each case, but in general is highly favorable" (Goldman et al. 1998, p. 1106)

Using the Psychostimulants:

- Use stimulants approved by the FDA
- Greater efficacy in decreasing ADHD symptoms vs placebo
STIMULANTS FDA-APPROVED FOR ADHD
- Adderall (amphetamine)( 3 and older)
- Adderall XR (amphetamine extended release)
- Vyvanse (lisdexamfetamine dimesylate extended release)
- Concerta (methylphenidate long acting)
- Daytrana (methylphenidate patch)
- Dexedrine (dextroamphetamine)
- Dextrostat (dextroamphetamine)
- Focalin (dexmethylphenidate)
- Focalin XR (dexmethylphenidate extended release)

STIMULANTS FDA-APPROVED FOR ADHD
- Metadate ER (Methylphenidate extended-release)
- Metadate CD (Methylphenidate extended-release)
- Methylin (Methylphenidate oral solution & chewable tabs)
- Ritalin (Methylphenidate)
- Ritalin SR (Methylphenidate extended-release)
- Ritalin LA (Methylphenidate long-acting)
- Quillivant XR

Stimulants continue to show efficacy in RCTs that have been done since 1985.
Motor Effects of Psychostimulants:
- Reduce activity to level that fits the context
- Decrease excessive talking, noise, and disruption
- Decrease fidgeting & finger-tapping
- Improve handwriting
- Improve fine-motor control

Social Effects of Psychostimulants:
- Reduce off-task behaviors
- Improve ability to play and work independently
- Reduce impulsivity
- Decrease intensity of behaviors
- Reduce bossiness
- Reduce verbal and physical aggression
- Improve socialization
- Reduce noncompliance and defiance with adults
- Improve parent-child interactions

Cognitive Effects of Psychostimulants:
- Improve effort and attention, especially to boring tasks
- Increase on-task behavior
- Reduce distractibility
- Reduce impulsivity
- Increase quantity and accuracy of academic work

Mina Dulcan M.D., Child and Adolescent Psychiatry 4th ed, 2012
Before treatment begins:
- Parent should agree to monitor medication
- Get cardiac history of patient and family
- Parents must attend follow up appointments
- Get baseline data from school

METHYLPHENIDATE
- Active ingredient in the majority of the stimulants in the US.
- Blocks reuptake of dopamine in the presynaptic neuron in the CNS & increase the neurotransmitters concentration in the synaptic cleft.
- 90% of radiolabeled MPH is recovered from the urine

MPH-IR
- Immediate-release form is absorbed quickly into systemic circulation.
- Effects may be seen in 30 minutes
- 3-5 hour duration; peak in plasma concentration at 90 minutes
- Usually dosed 3 times/day
- Initiate morning dose at 5 mg and titrate other 2 doses every few days
- Max is 20 mg tid
MultiModal Treatment of ADHD Study (MTA)

- NIMH funded and multisite study designed to evaluate treatments for ADHD (behavioral therapy, medications, and the combination of the two).
- A 14-month study with almost 600 children, ages 7-9 that were randomly assigned to 1 of 4 treatments:
  - Intensive Medication Management alone
  - Intensive Behavioral Treatment alone
  - A combination of both, or
  - Routine community care (as the control group)
- NIMH, MTA Study, Nov 2009; revised

Results of the MTA

- Published in December 1999 in Archives of General Psychiatry
- Combination treatment and Medication treatment alone (optimally titrated) were both significantly superior to intensive behavioral treatment alone and to routine community care in decreasing ADHD symptoms
- Benefits lasted for as long as 14 months
- NIMH, MTA Study, Nov 2009; revised

MTA Results contd

- Those that had difficulty also in other areas (anxiety, academic performance, parent-child relations, and social skills), combination treatment was consistently superior to routine community care. Medication or behavioral therapy alone were not.
- Children in combination treatment took lower doses of medication than children in med-only group
- Findings consistent across all 6 research sites
- NIMH, MTA Study, Nov 2009; revised
MTA Results Contd

- 289 children were randomized to medication group; 4% had discontinued the medication due to adverse effects
- ADVERSE EFFECTS INCLUDED:
  - Loss of appetite
  - Sleep Problems
  - Crying spells
  - Repetitive movements

MTA RESULTS CONTD.

- Physical growth of children slowed with medication during the 14 month treatment
  - However, 88% of the children were successfully treated.

Limitations on the MTA:

- Study done before the extended-release formulations on stimulants were as available.
- Study only lasted 14 mths and then referred back to community providers.

Long-acting Psychostimulants

- Convenience
- Better compliance
- Diminished rebound side-effects

Long-acting MPH

- Ritalin LA
- SODAS formulation (spheroidal oral drug absorption system)
- Can be opened and sprinkled
- Two pulse release system
- Efficacy of Ritalin LA for ADHD established in 1 controlled trial with 132 children (6-12 yo) who met criteria for ADHD (Wigal et al. 2004)

Long-acting MPH

- Concerta
- OROS delivery system that uses osmotic delivery system
- Duration of action is up to 12 hours (Swanson et al. 2004; Wolraich et al. 2001)
- IR MPH applied on outside of OROS cap to allow quicker onset of action for first 2 hours
- The osmotic pump delivers the rest of the med over a 10-hour span
Dexmethylphenidate
- Focalin and Focalin XR
- D-threo enantiomer of MPH
- IR form reaches maximum in the fasted state about 1-1.5 hours postdose
- Focalin XR is the extended-release form that has SODAS technology and has a bimodal release
- A study by Greenhill et al (2006) showed a significantly greater decrease in ADHD scores for youth taking the focalin xr vs placebo (103 pediatric patients from 6-17 yo)

Transdermal MPH
- Daytrana
- Absorbed after application, but blood levels do not peak until 7-9 hours later
- Duration of action is 11.5 hours or a 9-hour wear period.
- A double-blind and placebo-controlled study by McGough et al 2006) showed that children actively wearing the patch had significantly lower ADHD symptom scores and higher math scores for postdose hours 2-9.
- As effective as other long-acting MPH, but more frequent adverse effects.

AMPHETAMINE PSYCHOSTIMULANTS
- Dextroamphetamine (Dexedrine, lisdexamfetamine)
- Absorption is rapid
- Plasma levels peak 3 hours after ingestion
- Effects may be seen within 1 hour
- Lasts 4-6 hours
- Dosed twice/day
- Metabolized hepatically
AMPHETAMINE
PSYCHOSTIMULANTS

- Adderall and Adderall XR (amphetamine salt mixtures)
- Adderall XR is a dual-pulse capsule that includes both IR and extended-release beads
- No evidence that amphetamines has any advantages vs. MPH

Lisdexamfetamine dimesylate (Vyvanse)
- Prodrug
- Only minimal amounts of D-amphetamine are released when the medication is given parenterally
- It was produced this way to lessen the potential for abuse
- Two double-blind, placebo-controlled, and RCT (342 children with ADHD) showed significant reductions in ADHD, with mixed amphetamine salts and lisdexamfetamine dimesylate, vs. placebo (Biederman et al 2007a, 2007b)

Common Adverse Effects:
- Anorexia
- Weight loss or slowed weight gain
- Irritability
- Abdominal Pain
- Headaches
- Easy crying

Less Common Side Effects:

- Mildly elevated BP
- Insomnia
- Dysphoria
- Rebound overactivity and hyperactivity
- Skin picking and/or nail biting
- Allergic hives, rash, or conjunctivitis
- Transient motor tics

*Source: http://www.nimh.nih.gov*

FDA Warning on possible rare side effects

- In 2007, the FDA required that all makers of ADHD medications develop Patient Medication Guides that contain information about the risks associated with the medications. The guides must alert patients that the medications may lead to possible cardiovascular (heart and blood) or psychiatric problems. The agency undertook this precaution when a review of data found that ADHD patients with existing heart conditions had a slightly higher risk of strokes, heart attacks, and/or sudden death when taking the medications.

FDA Warning Cont:

- The review also found a slight increased risk, about 1 in 1,000, for medication-related psychiatric problems, such as hearing voices, having hallucinations, becoming suspicious for no reason, or becoming manic (an overly high mood), even in patients without a history of psychiatric problems. The FDA recommends that any treatment plan for ADHD include an initial health history, including family history, and examination for existing cardiovascular and psychiatric problems.

*Source: http://www.nimh.nih.gov*
In 2008, The American Academy of Pediatrics (supported by the American Academy of Child and Adolescent Psychiatry) issued a statement (Perrin et al. 2008) concluding that routine pretreatment cardiac tests are not currently indicated unless there is known/suspected cardiac disorder or symptoms.

- If there is any suspicion of cardiac dysfunction, an EKG & pediatric cardiology consultation should be requested before the start of any psychostimulant.

Child and Adolescent Psychiatry, 4th ed. 2012, pp268

Contraindications for Psychostimulant Use:

- Schizophrenia (or other acute psychosis)
- Glaucoma
- Recent Stimulant Drug Abuse
- Eating Disorders

Nonstimulants

- Atomoxetine (Strattera)
- Approved by FDA for treatment of ADHD in both kids and adults
- A selective NE reuptake inhibitor
- Rapidly absorbed
- Metabolized through CYP2D6 but excreted in urine.
- < 70 kg, start at 0.5 mg/kg/day in divided doses but may increase to 1.2mg/kg/day after 1 week (max 1.4mg/kg/day)
- May take few weeks for efficacy to be seen
- More coverage in mornings and evenings (unlike stimulants)
Atomoxetine – Adverse Effects:
- Somnolence
- Nausea
- Decreased appetite
- Vomiting

Atomoxetine – Black Box Warning:
**FDA warning that this med should be discontinued in those that develop jaundice or have dark urine or have laboratory evidence of liver injury**

**FDA warning based on report from Eli Lilly stating that 5 out of 1,800 youth in atomoxetine trials spontaneously reported SI( none of youth randomly assigned to placebo made such reports)**


Clonidine and Guanfacine
- L-2 presynaptic receptor agonist indicated for adult hypertension
- Nonstimulant treatment for ADHD children with aggression
- Used to be dosed tid, but now reformulated into KAPVAY(clonidine) (qd-bid dosing) and INTUNIV (guanfacine) (qd dosing)
- FDA approval for ADHD treatment in children
- KAPVAY also has a specific indication as add-on therapy to a stimulant
- Coverage in the mornings and evenings (unlike stimulants)
Choosing a Medication for ADHD:

- Difficult to predict drug response
- Majority of children with ADHD will respond to either MPH or dextroamphetamine
- No universally-agreed upon method for dosing with stimulants
- Nonstimulants are an option if pt has not tolerated 2 different stimulants, inadequate response of stimulants, unfavorable side effects, or parental preference

Clinical Pearls:

- Optimize dosage
- Regular appointment to monitor for treatment-emergent side effects
- Remain in regular contact with teachers/school

References: