UPMC

University of Pittsburgh
Medical Center

Children's Case Management
Module 2

Psychopharmacology for Children/Adolescents with Mental Illness

Program Description

The following module reviews the most frequent medications used to treat children and adolescents with mental illness. This will include stimulants, anti-psychotics, anti-depressants and mood stabilizers.

Educational Objectives

Upon completion of this section, you will be able to:

- Identify the various classes of psychopharmacologic agents presently being used
- Recognize the therapeutic and adverse effects of these medications on children and adolescents

Course Outline

- Use of Medications in Children
- Stimulants
- Antidepressants
- Antipsychotics
- Antidyskinetics
- Mood stabilizers

Issues Related to Children

- Most psychiatric medications lack FDA approval for use in children
  - Safety & efficacy in children are not established
  - Dosing information is extrapolated from adult studies & may be inadequate for children
- Consider dosage form availability
  - Can the child swallow tablets/capsules?
  - Are there alternatives such as patches or liquids?

Stimulants

- Used to treat
  - Attention Deficit – Hyperactivity Disorder (ADHD)

Epidemiology: ADHD

- Attention Deficit – Hyperactivity Disorder (ADHD) is the most commonly diagnosed child psychiatric disorder
- Prevalence in school-age children is 3-7%
- Boys are diagnosed more frequently than girls
- 75-95% of patients respond to stimulant therapy

What is ADHD?

- Signs of developmentally inappropriate inattention, hyperactivity & impulsivity
- Some symptoms must be present before age 7
- Symptoms must last more than 6 months and be observed in 2 or more settings
- Clinically significant impairment in social & academic functioning
- Symptoms are not the result of another disease

Three Subtypes of ADHD

- **Predominantly hyperactive-impulsive type** (that does not show significant inattention)
- **Predominantly inattentive type** (that does not show significant hyperactive-impulsive behavior) sometimes called ADD—an outdated term for this entire disorder
- **Combined type** (that displays both inattentive and hyperactive-impulsive symptoms)

Subtype: Hyperactive-Impulsive

- Fidgets with hands/feet
- Squirms in seat/leaves seat
- Has difficulty engaging in leisure activities quietly
- Often talks excessively
- Has difficulty awaiting turn
- Interrupts/intrudes on others
- Blurting out answers before hearing the whole question

Subtype: Inattention

- Fails to give close attention to details
- Difficulty maintaining attention in tasks
- Difficulty following instructions
- Avoids or is reluctant to complete school work
- Often becoming easily distracted by irrelevant sights and sounds
- Often skipping from one uncompleted activity to another

Subtype: Combined

- Six (or more) symptoms of inattention
- Six (or more) symptoms of hyperactivity-impulsivity
- Symptoms persist for at least six months
- Most common type of ADHD

Potential Co-Morbid Conditions

- Tourette's Syndrome
- Oppositional Defiant Disorder
- Conduct Disorder
- Anxiety and Depression
- Bipolar Disorder
- Learning Disabilities

Treatment Selection

- There is no single treatment that is the answer for every child
- Each child's needs and personal history must be carefully considered
- Side effects should be considered when making a medication selection

Symptom Management

Treatments have been shown to:

- Decrease hyperactivity & impulsivity
- Improve ability to focus, work & learn

FDA Approved Age for Use

- Ages 3 and Older
  - Adderall (amphetamine)
  - Dexedrine (dextroamphetamine)

FDA Approved Age for Use for Ages Six and Over

- Adderall XR (amphetamine)
- Concerta (methylphenidate)
- Cylert (pemoline)
- Daytrana (methylphenidate)
- Dexedrine Spansules (XR) (dextroamphetamine)
- Focalin / Focalin XR (dexmethylphenidate)
- Metadate / Metadate ER / Metadate CD (methylphenidate)
- Ritalin / Ritalin SR / Ritalin LA (methylphenidate)
- Vyvanse (lisdexamfetamine)

FDA Warning

- In Feb 2007, the FDA directed manufacturers of all drugs approved for the treatment of ADHD to develop patient medication guides to warn of possible cardiovascular and psychiatric adverse events and precautions that can be taken
- An FDA review of cases revealed reports of sudden death in patients with underlying serious heart problems or defects and reports of stroke & heart attack in adults with certain risk factors
- An FDA review also revealed an increased risk for drug-related psychiatric adverse events such as hallucinations, suspiciousness and manic behavior even in those without prior history

Methylphenidate (MPH)

- Dosing for immediate release products:
  - Initial dose for age 6 & older: 2.5mg-5mg twice daily (breakfast & lunch)
  - Increase by 5-10mg/day at weekly intervals
  - Consider a third dose, 4 hours after the second dose, but not after 5pm to prevent insomnia
- Maximum recommended dose: 60mg/day
- No difference in efficacy between sustained & regular release
- Supplied as: 5mg, 10mg, 20mg tablets; 2.5mg, 5mg, 10mg chewable tablets; 10mg and 20mg SR tablets; oral solution (5mg/5mL, 10mg/5mL)

Concerta® (Methylphenidate)

- Delivers immediate release, followed by steady release over several hours
- Medication is contained in a non-absorbable shell (shell may be found in stool)
- Peak blood levels: 6-8 hours after dose
- Duration of effect: 10-12 hours

Recommended Dosing Guidelines

- Initial dose in those new to MPH: 18mg/day
- Adjust dose in increments of 18mg in weekly intervals
- Maximum recommended dose (6-12yrs): 54mg/day
- Maximum recommended dose (13-17yrs): 72 mg/day
- Supplied as: 18mg, 27mg, 36mg, 54mg tablets
- Do not cut or chew tablets, swallow whole

Recommended Dose Conversion from MPH Regimens to Concerta®

Previous MPH Daily Dose	Concerta® Dose
5mg twice daily or three times daily; 20mg SR	18mg each morning
10mg twice daily or three times daily; 40mg SR	36mg each morning
15mg twice daily or three times daily; 60mg SR	54mg each morning

Metadate CD®

- Methylphenidate product
- Supplied as a capsule containing 2 types of beads
  - 30% immediate release
  - 70% sustained release
- Duration of effect: 9 hours
- Starting dose: 20mg
- Maximum dose: 60mg
- Supplied as: 10mg, 20mg, 30mg, 40mg, 50mg & 60mg capsules

Ritalin LA®

- Methylphenidate product
- Supplied as a capsule containing 2 types of beads
  - 50% immediate release
  - 50% sustained release
- Starting dose: 20mg
- Maximum dose: 60mg
- Supplied as: 10mg, 20mg, 30mg, 40mg capsules

Metadate CD® & Ritalin LA®

- May be swallowed whole
- Capsules may be opened & the contents sprinkled onto a tablespoon of applesauce (applesauce should not be warm)
- Must not be chewed
- The mixture must be used immediately and may not be stored
- Ritalin LA® should not be given with antacids

Daytrana®

- A methylphenidate transdermal system (patch)
- Apply to hip area daily in the morning 2 hours before an effect is desired
- Alternate sides of hip on a daily basis
- Remove after 9 hours (effects last another 2-3 hours after patch removal)
- Supplied as:10mg, 15mg, 20mg 30mg patches
- Patches expire 2 months after the package is opened

Side Effect Profile of MPH

- Most are dose-related & diminish after continued treatment
- Most common:
  - Loss of appetite
  - Insomnia
  - Weight loss
  - Abdominal pain
- Less frequent side effects: dizziness, rapid heart beat, headache, tics/jitteriness, priapism
- Black Box Warning: Abuse and dependence

Focalin® (dexmethylphenidate)

- Dosing for those on methylphenidate:
  - 1/2 of the total daily methylphenidate dose
- Dosing for those NOT on methylphenidate:
  - 2.5mg twice daily-increasing by 2.5-5mg weekly
- Should always be dosed twice daily at least 4hrs apart
- Supplied as: 2.5mg, 5mg, 10mg tablets

Focalin XR®

- Dexmethylphenidate sustained-release product
- Starting dose: 5mg daily
- Maximum recommended dose: 20mg
- May be opened & sprinkled on applesauce
- Do not cut, crush, or chew the capsule or its contents
- Supplied as: 5mg, 10mg, & 20mg capsules

Side Effect Profile of Dexmethylphenidate

- Twitching
- Rapid heart beat
- Loss of appetite
- Insomnia
- Nausea
- Abdominal pain
- Fever
- Weight loss (rare)

Cylert® (pemoline)

- Not first line due to potential liver toxicity - not commonly used
- Onset of action slower than other agents
- Once daily dosing
- ≥ 6 years: 37.5mg/day, increase by 18.75mg/day at weekly intervals; Maximum: 112.5mg
- Common side effects: weight loss, loss of appetite, insomnia

Amphetamine Products

Immediate Release	Sustained Release
Dexedrine® (dextroamphetamine sulfate)	Dexedrine Spansules® (dextroamphetamine sulfate)
Adderall® (dextroamphetamine sulfate/saccharate & amphetamine sulfate/aspartate)	Adderall XR® (dextroamphetamine sulfate/saccharate & amphetamine sulfate/aspartate)

Dexedrine® (dextroamphetamine)

- Equally effective as methylphenidate, but used second-line
- 3-5 years: 2.5mg/day, increase by 2.5mg/day in weekly intervals; Maximum: 40mg/day
- ≥ 6 years: 5mg once or twice daily, increase by 5mg/day in weekly intervals; Maximum: 40mg/day
- Long acting forms may be used once a day
- Dose in the morning with second dose in 4-6 hrs.
- Supplied as: 5mg & 10mg tablets; 5mg, 10mg, 15mg extended-release capsules

Adderall® (mixed amphetamine salts)

- 3-5 years: 2.5mg/day, increase by 2.5mg/day in weekly intervals; Maximum: 40mg/day
- ≥ 6 years: 5mg/day, increase by 5mg/day in weekly intervals; Maximum: 40mg/day
- Dose in the morning with second dose in 4-6 hrs.
- Supplied as: 5mg, 7.5mg, 10mg, 12.5mg, 15mg, 20mg, 30mg tablets

Adderall XR®

- Contains 2 types of beads
  - 50% immediate release; 50% sustained release
- Starting dose: 10mg
- Daily dosage may be raised in increments of 10mg at weekly intervals
- Maximum recommended dose: 30mg
- May open & sprinkle on apple sauce
- Supplied as: 5mg, 10mg, 15mg, 20mg, 25mg, & 30mg capsules

Side Effect Profile of Amphetamine Products

- Insomnia
- Abdominal Pain
- Loss of Appetite
- Rapid heart beat
- Tics

Vyvanse® (lisdexamfetamine)

- Newest stimulant for ADHD (Approved: Feb 2007)
- Starting Dose: 30mg given daily in the morning
- Maximum recommended dose: 70mg daily
- May be swallowed whole or the capsule may be opened & the contents dissolved in a glass of water
- Duration of effect: ~12 hours
- Supplied as: 30mg, 50mg, 70mg capsules

Side Effect Profile of Lisdexamfetamine

- Abdominal pain
- Dry mouth
- Nausea / vomiting
- Fever
- Weight loss
- Insomnia
- Irritability
- Tics
- Rash

Drug Interactions: Stimulants

MAO Inhibitors (MAOI)

- Antidepressants rarely used in children
- Avoid using stimulants within 2 weeks of using an MAOI
- Can cause hypertensive crisis

Strattera® (atomoxetine)

- Approved for ADHD for those 6 and older
- A non-stimulant, non-controlled substance
- A selective Norepinephrine re-uptake inhibitor
- Advantages
  - Prescriptions may be called to a pharmacy
  - Refills can be provided unlike with stimulants
  - No abuse potential
- May be discontinued without being tapered

Atomoxetine (Strattera®)

- Administer with caution in patients on Albuterol therapy due to potential elevation of cardiovascular effects
- Administer with caution in patients on blood pressure medications
- Carries a warning of potential liver toxicity
- New Black Box warning due to potential for suicidal ideation

Dosing Guidelines for Strattera®

Weight	Starting Dose	Target Dose
40-60lbs	18mg	25mg
63-93lbs	25mg	40mg
94-126lbs	40mg	60mg
127 +lbs	40mg	80mg

- Maximum recommended dose: 1.4mg/kg or 100mg-which ever is less

Atomoxetine (Strattera®)

- Can be given once daily in the morning or in 2 divided doses (morning & late afternoon or evening)
- Side effects (dose related):
  - decreased appetite, dry mouth, headache, dizziness, abdominal pain, nausea
- Drug Interactions: MAOI, Albuterol, Tricyclic Antidepressants
- Supplied as: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg capsules

Clonidine (Catapres®/Kapvay®)

- FDA approved for blood pressure control
- Dosing for ADHD: 0.05mg orally 3 -4 times a day, starting with 0.05 mg at bedtime to assess sedation
- Dosing must be individualized; Blood pressure must be monitored
- Side Effects: Dry mouth, depression, sedation, low blood pressure, fatigue, constipation
- Supplied as: 0.1mg, 0.2mg & 0.3mg tablets

Guanfacine (Tenex®/Intuniv®)

- Tenex (IR): FDA approved for blood pressure control
- Intuniv (ER): FDA approved for ADHD monotherapy or in combo with a stimulant
- Used if clonidine is not tolerated
- Starting dose: 1mg daily (extended release)
- Maximum dose: 4mg/day
- Side Effects: upset stomach, dry mouth, bad taste in mouth, low blood pressure, sedation, headache
  - More likely to occur with IR tablets
- Supplied as: 1mg & 2mg tablets

Antidepressants

Used to Treat:

- Depression
- Anxiety disorders
- Obsessive-compulsive disorder (OCD)
- Post-traumatic stress disorder (PTSD)
- Co-morbid states: conduct disorder, oppositional disorders, ADHD

Epidemiology: Depression

- Prevalence:
  - 2% in children
  - 4-8% in adolescents
- Anxiety, somatic complaints, auditory hallucinations, temper tantrums, and behavioral problems are more likely to occur in children with depression
- Children in middle-to-late childhood display an increased cognitive component to dysphoria, low self-esteem, guilt, and hopelessness

Epidemiology: Depression

- Adolescents are more likely to exhibit sleep and appetite disturbance, delusions, suicidal ideation and attempts, and functional impairment than younger patients, and fewer vegetative symptoms and greater irritability than adults
- Suicide is a leading cause of death in older adolescents & in children aged 5-14
- Relapse risk is high

Depression Symptoms

- **S**leep patterns altered
- **I**nterests gone
- **G**uilt
- **E**nergy or fatigue
- **C**oncentration/memory problems
- **A**ppetite increased or decreased
- **P**sychomotor changes: agitation or retardation
- **S**uicidal thoughts; thoughts of death

The Alphabet Soup of Antidepressants

- MAOI – monoamine oxidase inhibitors
- TCA – tricyclic antidepressants
- SSRI - selective serotonin reuptake inhibitors
- SNRI - selective norepinephrine reuptake inhibitors
- NRI/SRI – norepinephrine and serotonin reuptake inhibitors

FDA Warning

- All antidepressants carry a black box warning stating that suicide & suicidal ideation in children, adolescents & young adults is increased with antidepressant use
- Risk should be balanced with clinical need
- Patients should be closely monitored by healthcare professionals & family members for these behaviors

Tricyclic Antidepressants (TCAs)

Traditional tricyclic antidepressants

- imipramine (Tofranil) - 1950s
- desipramine (Norpramin, Pertofrane)
- amitriptyline (Elavil)
- protriptyline (Vivactil)
- nortriptyline (Aventyl, Pamelor)
- doxepin (Adapin, Sinequan)

TCAs

- Mechanism of Action: precise mechanism is unknown. TCAs immediately block reuptake of monoamine neurotransmitter reuptake (both norepinephrine and serotonin) to varying degrees.
- Lost place as first-line therapy due to side effects which vary in degree with any particular TCA
- Despite lag in therapeutic effect, side effects may occur immediately
- Dose-Related Side Effects/Toxicity:
  - At Therapeutic Doses: Weight gain, some sexual dysfunction, lowers seizure threshold
  - At Toxic Doses: Cardiovascular toxicity (conduction delays, arrhythmias), severe anticholinergic effects, convulsions

TCA Drug Interactions

- Can be displaced by other highly bound drugs (TCA levels ↑)
  - Phenytoin
  - Aspirin
  - Phenothiazines
- Metabolism can be inhibited by (TCA levels ↑)
  - Antipsychotics
  - Oral contraceptives
  - SSRIs

TCA Drug Monitoring

- Narrow Therapeutic Range with dose-related toxicities
- 3-5% of patients have insufficient enzymes to metabolize TCA drugs; may develop life-threatening toxicities
- Monitor serum drug levels
- Draw levels 10-12 hours after last dose

SSRIs

- First line antidepressant for most patients
- Block presynaptic reuptake of serotonin
- Observed therapeutic effect delayed by several weeks
- Adverse effects apparent within first week
- Lower risk of death in an overdose than with TCAs

Available SSRIs

- Fluoxetine (Prozac®) - first SSRI approved (1987)
  - Approved for use in children for depression & OCD
- Sertraline (Zoloft®)
  - Approved for use in children for OCD
- Fluvoxamine (Luvox®)
  - Approved for use in children for OCD
- Paroxetine (Paxil®)
- Citalopram (Celexa®)
- Escitalopram (Lexapro®)
  - Approved for use in children with MDD

SSRIs

- No more effective than TCAs; however, more favorable side-effect profile
- Less cardiotoxicity than TCAs
- Most SSRIs administered in the morning (may cause insomnia); Paroxetine is the exception (give at bedtime; can be sedating)
- Delayed efficacy - may be somewhat less than TCA's – Take 4-6 weeks to see full effects

SSRIs

- Mechanism of action - selective blocking of serotonin reuptake into nerve terminals and delayed adaptive changes in the CNS = long term increase of serotonin
- Adverse Side Effects:
  - GI disturbances (nausea, diarrhea, cramping, heartburn)
  - CNS excitation or stimulation (restlessness, insomnia and anxiety) – paroxetine which may cause sedation
  - Significant anorexia and weight loss during early treatment; possible weight gain with long-term use
  - Decreased libido and significant sexual dysfunction (anorgasmia, ejaculatory delay, impotence)
  - Withdrawal syndrome has been described that includes nausea, dizziness, anxiety, tremor and palpitations

SSRIs and Drug Interactions

- Numerous potential drug interactions due to inhibition of other drugs by CYP450 enzymes
- Citalopram (Celexa®) has the least potential for drug interactions
- SSRI + Monoamine Oxidase Inhibitors = Serotonin Syndrome (rapid mental status changes, seizures, coma, and death)

Other Clinical Uses for SSRIs

- Generalized anxiety disorder
- Social phobia
- Panic disorder
- Obsessive-compulsive disorder
- Bulimia nervosa
- Migraine headaches
- Premenstrual Syndrome (PMS) & Premenstrual Dysphoric Disorder (PMDD)
- Posttraumatic stress disorder
- Seasonal affective disorder (SAD)
- Post-partum depression

SSRI Dosage Forms

Drug Name	Tablet	Capsule	Liquid
Fluoxetine	10mg	10mg, 20mg, 40mg 90mg (Prozac Weekly)	20mg/5ml
Sertraline	25mg, 50mg, 100mg		20mg/ml *contains 12% alcohol
Fluvoxamine	25mg, 50mg, 100mg		
Paroxetine	10mg, 20mg, 30mg, 40mg Paxil CR – 12.5mg, 25mg, 37.5mg		10mg/5ml
Citalopram	10mg, 20mg, 40mg		10mg/5ml
Escitalopram	5mg, 10mg, 20mg		5mg/5ml

Miscellaneous Antidepressants

- Bupropion (Wellbutrin)
- Trazadone (Desyrel)
- Venlafaxine (Effexor)
- Mirtazapine (Remeron)
- Nefazadone (Serzone)
- Duloxetine (Cymbalta)

Bupropion (Wellbutrin®)

- Unique mechanism of action
  - Weakly blocks reuptake of dopamine; possibly some blockade of norepinephrine and serotonin reuptake.
- Three formulations available for depression
  - Wellbutrin 200-450 mg/day (TID)
  - Wellbutrin SR 150-400 mg/day (BID)
  - Wellbutrin XL 300-450 mg/day (daily)
  - All formulations have very specific restrictions on how much can be given per dose & how far apart doses must be spaced.
- Also approved for ADHD and smoking cessation (Zyban®)

Bupropion Side Effects

- Generally well tolerated
- Low incidence of sedation, hypotension and weight gain
- Unlike other antidepressants, few sexual side effects
  May cause restlessness, insomnia (not given after 5pm), anxiety (structurally similar to amphetamine) or precipitate psychotic episodes in susceptible individuals
- High risk of seizure activity (0.5%) at dose of 450 mg/day; give in divided doses

Bupropion (Wellbutrin®)

- Drug Interactions:
  - Contraindicated with MAOIs
  - Caution with drugs that affect CYP3A4,CYP2D6 (specific liver enzymes)
  - Caution with drugs that lower seizure threshold
- Contraindicated in with patients with:
  - Seizure disorder
  - Bulimia or anorexia nervosa

Bupropion (Wellbutrin®)

- Supplied as:
  - Bupropion: 75mg, 100mg tablets
  - Bupropion SR: 100mg, 150mg, 200mg tablets
  - Bupropion XL: 150mg, 300mg tablets
  - Do not cut, crush or chew SR or XL tablets

Trazodone (Desyrel®)

- Introduced in the early 1980s
- Mechanism of Action
  - Blocks serotonin reuptake; antagonist at 5-HT2 receptors
  - Partial agonist at 5-HT1A receptors
  - Little effect on norepinephrine uptake, but may stimulate norepinephrine release
- Dosage: 150mg/day in divided doses; may increase dose by 50mg every 3-4 days to max 400mg/day
- Used more often to induce sleep

Trazodone (Desyrel®)

- Side effects
  - Sedation - low dose used for insomnia
  - GI upset (nausea and vomiting)
  - Dry mouth, blurred vision
  - Orthostatic hypotension
  - Priapism (sustained erection)- rare but serious

Venlafaxine (Effexor® and Effexor XR®)

- Mechanism of Action
  - Blocks reuptake of norepinephrine and serotonin; weakly inhibits DA reuptake; little or no effect at muscarinic, adrenergic or histaminic receptors
  - Works like SSRI at lower doses (<200mg/day)
- Dosing
  - Direct dosing conversion from Effexor to Effexor XR
  - Initiate dose at 37.5mg then increase by 75mg every 4-5 days to a max daily dose of 225mg
  - XR formulation: increased compliance, may decrease GI side effects; do not cut, crush or chew the capsule

Venlafaxine (Effexor® and Effexor XR®)

- Side Effects
  - Restlessness and insomnia
  - Nausea and vomiting
  - Sexual dysfunction
  - Increase in blood pressure in approximately 5% of patients; dose-dependent (> 300mg/day)
- Drug Interactions
  - Minimal; some potential for interaction with agents metabolized by CYP2D6 (clozapine, paroxetine, etc.)

Desvenlafaxine (Pristiq®)

- Mechanism of Action
  - Potent, selective serotonin and norepinephrine reuptake inhibitor (SNRI) that potentiates the neurotransmitter activity in the central nervous system (CNS)
- Dosing
  - 50mg once daily (recommended dosing)
  - Possibility to increase dosing to 50mg twice daily or 100mg once daily
  - Renal dosing necessary

Desvenlafaxine (Pristiq®)

- Side Effects
  - Restlessness and insomnia
  - Nausea and vomiting
  - Sexual dysfunction
  - Increase in blood pressure in approximately 1-2% of patients

Duloxetine (Cymbalta®)

- First drug approved for treatment of diabetic peripheral neuropathy
- Mechanism of Action
  - Inhibits the reuptake of both NE and 5-HT (SRI and NRI)
- Dosage: 30-120 mg/day
- Side Effects
  - nausea, dry mouth, fatigue and insomnia

Mirtazapine (Remeron®)

- The first of a new class of antidepressants
- Mechanism of Action
  - antagonist of central presynaptic α2-adrenergic receptors (increases norepinephrine and serotonin release)
  - Blockade of 5-HT2 and 5-HT3 receptors
  - Long acting (once daily administration)
- Dosing
  - Initiate at 15mg; increase to target range of 15-45mg
  - Long acting (once daily administration); Bedtime dosing preferred
  - Clearance is decreased in both renally/hepatically impaired patients and the elderly

Mirtazapine (Remeron ®)

- Side Effects
  - Sedation - blockade of histamine receptors, dose at bedtime
  - Significant weight gain, increased appetite/lipids

- Drug Interactions:
  - Allow 14 days between stopping an MAOI and starting mirtazapine and vice versa
  - Alcohol/benzodiazepines increase sedation

Nefazodone (Serzone®)

- Structurally similar to trazodone
- Mechanism of Action
  - Blocks serotonin reuptake; also acts an antagonist at 5-HT2 receptors
  - Partial agonist at 5-HT1A receptors
- Therapeutic dose range 300-600mg/day
- Side Effects: Nausea, constipation, blurred vision
  - Black box warning – potential life-threatening liver failure (1/250,000 per year)
- Drug Interactions
  - Inhibits CYP3A4 = many potential drug interactions
  - antihistamines, benzodiazepines, digoxin, etc.

Miscellaneous Antidepressants

Drug Name	Tablet	Capsule	Liquid
Trazodone	50mg, 100mg, 150mg		
Venlafaxine	25mg, 37.5mg 50mg, 75mg, 100mg	Effexor XR-37.5mg, 75mg, 150mg	
Duloxetine		20mg, 30mg, 60mg Extended Release	
Mirtazapine	15mg, 30mg, 45mg Tablets & dissolving tablets		
Nefazodone	50mg, 100mg, 150mg, 200mg, 250mg		

Monoamine Oxidase Inhibitors

- Inhibit the metabolic degradation of monoamines
  - MAO-A - norepinephrine, serotonin, and tyramine metabolism
  - MAO-B - selective for dopamine metabolism
- Indicated primarily for "atypical depression" (chronic fatigue, oversleeping, and phobic anxiety).
- Takes 2-3 weeks for effect
- May be helpful for patients who do not respond to or cannot tolerate other types of antidepressants…considered LAST RESORT due to high risk of hypertensive crisis
- Rarely used in children

MAOI Side Effects/Interactions

Side Effects

- Dizziness
- Blurred vision
- Weight gain
- Urinary hesitancy
- Insomnia

Drug Interactions

- Other antidepressants
- Pseudoephedrine
- Meperidine
- Atomoxetine

Food Interactions

- Tyramine-free diet should be maintained to avoid hypertensive crisis

- Foods high in tyramine include:
  - Aged cheeses
  - Beer
  - Aged meats
  - Avocados
  - Fava beans

EmSam®
(selegiline transdermal)

- Approved for treatment of Major Depressive Disorder in adults (Feb 2006)
- No dietary restrictions for the 6mg strength
- Onset of effect in a few days
- Patch applied to a dry, non-hairy area on the upper torso or arm daily
- Supplied as: 6mg, 9mg & 12 mg patches
- Side effects: site reactions, orthostatic hypotension

Antipsychotics

- Used to treat:
  - Psychosis
  - Bipolar disorder
  - Agitation & violent behavior
- Classification of Antipsychotics:
  - Traditional or typical agents (1950 to 1990)
  - Atypical agents (or second generation antipsychotics)
  - Third generation antipsychotics

Traditional or Classic Antipsychotics

- Primarily block dopamine receptors
- Therapeutic effects begin when 70% of D2 receptors are blocked
- Alleviate mainly positive symptoms
- Extrapyramidal side effects (EPS) seen at higher D2 occupancies
- Tardive Dyskinesia (TD) with long term use

Atypical or Second Generation

- Block more than one type of receptor
- Greater affinity for 5-HT than D2
- Alleviate positive & negative symptoms; possibly help neurocognitive deficits
- Less or no EPS or TD
- Can start treatment earlier in disease

Third Generation

- In 2003, aripiprazole (Abilify) introduced as the 7th atypical antipsychotic

- Unique synaptic actions, making it the first of a third generation of antipsychotic drugs
  - Not a dopamine antagonist, but rather a partial agonist of D2 receptors; “stabilizes” hyper and hypoactivity
  - Also, 5HT2 antagonist and partial agonist at 5HT1A

Clinical Indications for Antipsychotics

- Psychosis
  - Schizophrenia
  - Schizoaffective disorder
  - Bipolar disorder
  - Acute psychotic symptoms (violence/agitation) or behavioral disturbances related to Tourette's, Senile Dementia, Alzheimer's Disease, Autism

Symptom Domains

- Positive symptoms
  - Abnormality or exaggeration of normal function
  - Hallucinations, delusions, incoherence, loose associations, disorganized behavior
  - More easily controlled with antipsychotics

- Negative symptoms
  - Loss or decrease in social function
  - More persistent and less responsive to antipsychotic meds
  - Diminished and distorted capacity to process information and draw logical conclusions

Mechanism of Action: Traditional Agents

- Principally act via blockade of dopamine receptors
- Five subtypes of DA receptors have been described
  - Antipsychotic activity of the classical agents correlates best with D_2 receptor blockade
  - D_2 receptor blockade in the extrapyramidal tracts, and hypothalamus/pituitary account for many side effects of antipsychotics such as movement disorders and endocrine imbalances.
  - Other side effects are related to interactions with other neurotransmitters

Contraindications/Drug Interactions

- May be contraindicated in patients with Parkinson's Disease, hepatic failure, hypotension, bone marrow depression, or those prescribed CNS depressants

- Drug Interactions
  - Additive with CNS depressants or anticholinergic meds
  - Potential for increased metabolism when administered with agents that induce hepatic enzymes.

Adverse Effects: Traditional agents

- High therapeutic index with respect to mortality
- Overdoses rarely fatal, except with thioridazine (cardiotoxic)
- Side effects routinely occur at therapeutic doses; extensions of pharmacological actions
  - Sedation
  - Extrapyramidal Effects (dystonia, akathisia, parkinsonism)
  - Tardive Dyskinesia

Adverse Effects: Traditional agents

Sedation

- Common, especially with low potency drugs
- Due to activity at α1-adrenergic and histamine receptors
- Give as a single dose at bedtime
- Usually decreases with long term treatment

Akathisia

- Affects 20% of patients
- Intense motor restlessness and agitation
- Usually reversible
- Unresponsive to anticholinergics, treat with benzodiazepine or beta blockers

Acute Dystonia

- Affects 5% of patients
- Uncontrollable movements and distortions of the face, head and neck
- Often a results of large antipsychotic doses or rapid increases in dose
- Usually reversible
- Treat with benztropine (Cogentin) or diphenhydramine (Benadryl) and temporarily discontinue antipsychotic

Tardive Dyskinesia (TD)

- Occurs in 20-40% of chronically treated patients.
- Abnormal jerky, movements of the face and tongue. Poorly understood and unpredictable though thought to be due to D2 receptor supersensitivity.
- No treatment. May be irreversible. If signs of TD develop, reduce dose or discontinue the antipsychotic and eliminate all drugs with central anticholinergic action (antidepressants) or switch to clozapine.
- Prevention of TD is key! Give minimally effective doses, for limited time if possible.

Neuroleptic Malignant Syndrome (NMS)

- Rare medical emergency; affects 1% of patients but 10% of cases are fatal
- NMS is more common in males and 80% of cases occur in patients under 40
- Hyperthermia or fever, diffuse muscular rigidity and severe EPS, fluctuating levels of consciousness
- Treatment is supportive (rehydration, body cooling, discontinue antipsychotic)

Other Adverse Effects

- Cholestatic jaundice due to biliary obstruction
- Dermatological reactions – allergic reaction, increased sensitivity to the sun
- Ocular
  - opacities of the cornea and lens with chlorpromazine
  - decreased vision or blindness with high-dose thioridazine
- Reproductive effects
  - in women, amenorrhea and increased libido
  - in men, decreased libido and gynecomastia

Typical Antipsychotics

Drug Name	Tablet	Liquid	Short-acting Injection	Long-acting Injection
Chlorpromazine	10mg, 25mg, 50mg, 100mg, 200mg		25mg/ml	
Fluphenazine	1mg, 2.5mg, 5mg , 10mg	5mg/5ml	2.5mg/ml	25mg/1ml
Haloperidol	0.5mg, 1mg, 2mg, 5mg, 10mg, 20mg	2mg/ml	5mg/ml	50mg/ml 100mg/ml
Perphenazine	2mg, 4mg, 8mg, 16mg			

The Next Generations

- From 1975 to 1989, not a single new antipsychotic was marketed in the US
  - Clozapine – 1990
  - Risperidone – 1994
  - Olanzapine – 1996
  - Quetiapine – 1999
  - Ziprasidone – 2000
  - Paliperidone - 2007
  - Asenapine - 2009
  - Iloperidone – 2009
  - Lurasidone - 2011
  - Aripiprazole – 2003

Second Generation

Third Generation

Newer Antipsychotic Agents

- Newer agents have greater potency and less side effects
- Still only partially effective for most and ineffective for some patients
  - 30% inadequate or poor response (conventional treatment)
  - 60% relapse within 1 year of treatment
  - Estimated rate of noncompliance between 11-80%
- Generally trial and error approach with goal of decrease relapse rate by two-thirds to three-quarters compared to no treatment

"Atypical" Antipsychotics

- Compared to "classical" agents
  - Wider range of CNS receptor interactions (particularly 5-HT2 receptors)
  - Different adverse effect profile
- As a group, all produce less EPS and are less likely to produce tardive dyskinesia (TD)
- More effective in reducing "negative" symptoms of schizophrenia than the older agents

Clozapine (Clozaril®)

- Prototype “atypical” antipsychotic
- FDA approved in 1989
- Mechanism of Action
  - Binds multiple receptors (DA, 5HT, Ach…)
  - Greater 5-HT2 than D2 blockade defines “atypical”

Clozapine (Clozaril®)

- Not indicated as first-line for schizophrenia due to hematological effects (can decrease white blood cell count--intense monitoring required)
- Patient must have failed standard therapy with minimum of two other antipsychotics
  - insufficient effectiveness
  - signs of TD or other intolerable side-effects
- Clozapine salvages half of those patients who are considered treatment refractory

Clozapine (Clozaril®)

- Dosing (adults):
  - Initially, 12.5mg daily or twice daily
  - Increase daily of 25-50mg/day
  - Target dose 300-450mg/day by 2 weeks
  - Subsequent dosage increases should be made no more than 1-2 times/week
- Safety and effectiveness in pediatric and adolescent patients have not been established

Clozapine (Clozaril®) Dosing

Therapeutic Range

- Response between 300-600mg/day
- May be increased to 900mg/day

Discontinued Treatment

- Gradual reduction over 1-2 week period
- Abrupt discontinuation - observe recurrence of psychotic symptoms

Adverse Effects: Clozapine (Clozaril®)

- Sedation (40%)
- Weight gain (80%) – can be significant
- Constipation (30%)
- Agranulocytosis (1 - 2%)
  - Usually develops within the first 3 months of tx
  - Frequent monitoring of white blood cell counts required
  - Monitor for fever, sore throat, cellulitis
- Seizures (3.5%)

Risperidone (Risperdal®)

- Unique chemical structure
- Potent blockade of D2 and 5HT2 receptors
- Improved control of psychotic symptoms with minimal EPS at therapeutic doses
- Not associated with the hematological and seizure risks of clozapine
- Pediatric/adolescent uses approved by the FDA:
  - Schizophrenia in patients 13 yrs and older
  - Short-term treatment of manic or mixed episodes of bipolar I in patients 10 yrs and older
  - Treatment of irritability associated with autistic disorder in patients 5 yrs and older
  - PDD and behavioral disorders in patients 4 yrs and older – not FDA approved.

Risperidone (Risperdal®)

- Dosing (adults):
  - Initial: 1mg twice a day
  - Weekly dosage increases of 1-2mg until 3mg twice a day
  - Doses above 6mg twice a day no more effective, more EPS
- Target Dose Ranges (adults):
  - Schizophrenia: 4-16mg/day
  - Bipolar mania dosing: initial 2-3mg QD, with dose adjustments made at intervals of at least 24 hours up to 6mg/day
  - Elderly, severe renal/hepatic impairment start doses at 0.5mg twice a day (1.8mg/day)

Risperidone (Risperdal®)

- Dosing (pediatrics/adolescents):
  - Schizophrenia: 0.5 mg once daily, adjust doses by 0.5-1 mg at intervals of no less than 24 hrs to a max recommended dose of 3 mg/day
  - Bipolar I Disorder: 0.5 mg once daily, adjust doses by 0.5-1 mg at intervals of no less than 24 hrs to a max recommended dose of 2.5 mg/day
  - Autistic Disorder (irritability): 0.5 mg once daily (or half the daily dose administered twice daily), adjust at an interval of 4 days to 1 mg daily, increasing by increments of 0.5 mg as clinically needed
  - Autistic Disorder (irritability): use ½ of the above dosing for patients under 20kg in body weight

Risperidone Consta™

- Long acting depot formulation
- Initial dose (adults): 25mg IM every 2 weeks
- Max dose (adults): 50mg IM every 2 weeks
- Three week lag in effect, requires overlap of oral risperidone
- Dose adjustments should not be made more than once a month due to 3 week lag period
- Once reconstituted into the syringe, stable for only 6hrs
- Safety and effectiveness in pediatric and adolescent patients have not been established

Paliperidone (Invega®)

- Active metabolite of risperidone
- Not FDA approved for pediatric use
- Initial dose: 6mg daily (morning)
- Increase in increments of 3mg up to a recommended maximum of 12mg
- Must be swallowed whole
- Medication is contained in a non-absorbable shell. (Shell may be found in stool.)

Paliperidone (Invega®)

- Side Effects:
  - EPS
  - Elevated prolactin levels
  - Dizziness
  - Rapid heart beat
  - Somnolence
  - Nausea
- Drug Interactions
  - Paliperidone may antagonize levodopa
  - Additive CNS depression may occur with alcohol use
  - Additive risk of low blood pressure may occur with other medications with this effect

Paliperidone Palmitate (Invega Sustenna®)

- Long acting depot injection
- Dosing (adults):
  - 234 mg IM once, then 156 mg IM 7 days later
  - Initiate 117 mg IM injections monthly (every 28 days) thereafter (+/- 7 days)
  - Oral overlap is not required
- Consult medication guide for more accurate dosing if patients have missed their dosing window
- Safety and effectiveness in pediatric and adolescent patients have not been established, but currently are being studied.

Olanzapine (Zyprexa®)

- Structurally and pharmacologically similar to clozapine; agranulocytosis (decreased white blood cells) has not yet been reported

- Mechanism of Action
  - Completely blocks 5HT2 at low doses (5 mg)
  - D2 blockade increases with higher doses

Olanzapine (Zyprexa®) Dosing

- Initial dose 5-10mg daily
- Once a day dosing - usually bedtime
- Efficacy range 10-20mg/day
- Dosage adjustments 5mg increments at intervals of no less than 1 week
- Safety of doses above 20mg/day not evaluated

Olanzapine (Zyprexa®)

Indications

- Schizophrenia ≥13 yo
- Bipolar disorder ≥ 10 yo (monotherapy or combination therapy with lithium or valproate)
- Agitation associated with schizophrenia and Bipolar I Mania

Side Effects

- May produce mild sedation, occasional EPS, and weight gain in some patients
- Less impact on prolactin; no agranulocytosis

Dosage Formulations

- Injectable IM immediate-release
  - Acute agitation in patients already on another oral antipsychotic--not a substitute for oral
  - Dose: 10mg q2h up to 3 doses in 24 hours. Single dose not to exceed 10mg. Dosing in elderly can be 5mg or 2.5mg
  - Vials are single dose only and must be mixed prior to administration

Zyprexa Relprevv®

- Long-acting depot injection
  - For schizophrenia in adults ONLY
  - Dosing: 210mg, 300mg every 2-4 weeks or 405mg every 4 weeks w/oral overlap for 3 mos
- Patient Care Program (REMS)
  - Risk of severe sedation and/or delirium that could lead to coma or death (risk inc with each injection)
  - Patient must be monitored for 3 hrs post-injection
  - Prescriber, healthcare facility, patient, and pharmacy must be enrolled

Quetiapine (Seroquel®)

- Structurally related to clozapine
- 5HT2 > D2 blockade
- Clinical Indications
  - Schizophrenia
  - Bipolar mania
  - Not indicated for SLEEP!

Quetiapine (Seroquel®)

- No clinically significant cardiac arrhythmias or alterations in cardiac intervals
- Limited weight gain (~ 5 lb), mainly during the early weeks of treatment
- Lens changes in patients on long term therapy – eye exams every 6 months recommended
- Not indicated for SLEEP!

Quetiapine (Seroquel®) Dosing

- Treatment of Manic bipolar I disorder in patients 10-17 yrs old and schizophrenia in patients 13-17 yrs old
- Initial dose 25mg twice a day
- Titrate to dose range of 300-400mg/day by day 4
- Rate of titration and dose may need to be adjusted in hepatically impaired and elderly
- Effective at doses from 150mg-750mg/day- given in split doses, safety of doses > 800mg/day not established
- Safety and efficacy not established in pediatric patients younger than 10 years

Adverse Effects: Quetiapine (Seroquel®)

- Headache 21%
- Agitation 20%
- Somnolence 18%
- Dizziness 11%
- Dry mouth 9%
- Weight gain 5%

Ziprasidone (Geodon®)

- Structurally similar to risperidone
- Blocks 5HT2 and DA receptors similar to other atypicals
- Unique receptor actions
  - Agonist at 5HT1A receptor (a “buspirone-like” action)
  - Moderately blocks 5-HT and NE reuptake
- Improves depressive and negative symptoms

Ziprasidone (Geodon®) Dosing

- Starting dose: 40mg/day in divided doses
- Dosing range 40-160mg/day (20-80mg bid)
- Administered twice a day with food (>500 cal)
- Steady state achieved within 1-3 days
- No dosing adjustment for renal or mild-moderate hepatic impairment
- Safety and effectiveness in pediatric and adolescent patients have not been established

Adverse Effects: Ziprasidone (Geodon®)

- EPS 14%
- Somnolence 14%
- Nausea 10%
- Constipation 9%
- Dyspepsia 8%
- Dizziness 8%
- More proarrhythmic properties than other atypicals; Absence of significant weight gain

Ziprasidone (Geodon®) Indications

- Not approved for use in kids
- Schizophrenia
- Bipolar I mania
- Acute agitation in schizophrenic patients
  - First atypical approved for IM use for acute agitation- 2003

Ziprasidone (Geodon®) Injection

- IM: 10-20mg daily with a max of 40mg daily
- Can administer 10mg IM q2h, or 20mg q4h
- IM for more than 3 consecutive days has not been studied
- Long-term therapy: switch to oral
- Co-administration of IM and PO not recommended
- Less side effects, more effective in reducing acute symptoms than IM haloperidol

Asenapine (Saphris®)

- Dopamine-2 (D2) and serotonin type-2 (5HT2) receptor antagonist

- Sublingual formulation
  - Place under tongue and allow to dissolve completely
  - Instruct patient not to eat or drink for 10 minutes following administration
  - Bioavailability of the drug is minimal if swallowed

Asenapine (Saphris®)

- Indications:
  - Schizophrenia
  - Bipolar I Disorder
  - Safety and effectiveness in pediatric patients have not been established
- Dosing (adults):
  - 5 mg sublingually twice daily
  - Max of 10 mg sublingually twice daily
  - Severe hepatic impairment: not recommended

Iloperidone (Fanapt®)

- Dopamine-2 (D2) and serotonin type-2 (5HT2) receptor antagonist

- Indications:
  - Schizophrenia
  - Safety and effectiveness in pediatric and adolescent patients have not been established

Iloperidone (Fanapt®)

Side effects:

- Dry mouth
- Weight gain
- Tachycardia
- Hypotension (orthostatic)
- Seizure (may lower seizure threshold)

Iloperidone (Fanapt®)

- Dosing (adults): *Available as a titration pack*
  - Day 1: 1 mg twice daily
  - Day 2: 2 mg twice daily
  - Day 3: 4 mg twice daily
  - Day 4: 6 mg twice daily
  - Day 5: 8 mg twice daily
  - Day 6: 10 mg twice daily
  - Day 7: 12 mg twice daily
- Target dose of 6 – 12 mg twice daily

Lurasidone (Latuda®)

- High affinity dopamine (D2) and serotonin (5-HT2A & 5-HT7) antagonist; Moderate affinity alpha-adrenergic antagonist; partial 5-HT1A agonist
- Major substrate of CYP3A4 metabolism→ multiple drug interactions with both inducers and inhibitors

Lurasidone (Latuda®)

- Indications/Dosing
  - Safety and efficacy not established in pediatric patients
  - Schizophrenia – 40 mg daily up to 160 mg daily
  - Bipolar Disorder, depression – 20 mg daily up to 120 mg daily; efficacy not established for use beyond 6 weeks
- Must be given with at least 350 calories of food to be effective

Lurasidone (Latuda®)

- Side Effects:
  - Drowsiness (8-27%)
  - EPS (14-26%); akathisia (6-22%)
  - Inc TRG, glucose, cholesterol (10-14%)
  - N/V
  - Diarrhea
  - Inc prolactin (more so in women)

Aripiprazole (Abilify®)

- Introduced in 2003 – new hope for Schizophrenia; extolled as a "third generation" antipsychotic due to unique pharmacology
- Mechanism of Action
  - Partial agonist at D2 receptors and 5HT1A receptors
  - Antagonist at 5HT2A receptors
- Treats positive and negative symptoms, relieves anxiety, depression, and cognitive symptoms
- Also approved to treat Bipolar I disorder- mixed/manic, Autistic disorder, Tourette's syndrome, and MDD-adjunct

Aripiprazole (Abilify®) Dosing

- Initial dose: 10 or 15mg orally daily (adults); 2-5 mg orally daily (6-17 yo)
- Effective dose range 10mg-30mg/day
- Dose increases could not be made before 2 weeks, the time needed to reach steady-state
- Abilify Maintena (long-acting injection)
  - 400mg IM = 20mg PO
  - For Schizophrenia in adults ONLY
  - For gluteal injection ONLY
  - Oral overlap required with any antipsychotic for 14 days

Adverse Effects: Aripiprazole (Abilify®)

- Minimal weight gain or sedation
- No EPS even at high doses
- No prolactin elevation or QT prolongation
- Common side effects
  - Headache
  - Insomnia
  - Nausea
  - Constipation

Atypical Antipsychotics

Drug Name	Tablet	Dissolving Tablet	Liquid	Short-Acting Injection	Long-Acting Injection
Clozapine	25mg, 50mg, 100mg, 200mg	25mg, 100mg			
Olanzapine	2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg	5mg, 10mg, 15mg, 20mg		10mg vial	Zyprexa Relprevv: 210mg,300 mg, 405mg
Risperidone	0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4mg	0.5mg, 1mg, 2mg, 3mg, 4mg	1mg/1ml		Risperdal Consta: 12.5mg, 25mg, 37.5mg, 50mg
Quetiapine	25mg, 50mg, 100mg, 200mg, 300mg, 400mg				
Quetiapine XR	200mg, 300mg, 400mg				

Atypical Antipsychotics

Drug Name	Tablet / Capsule	Dissolving Tablet	Liquid	Short-Acting Injection	Long-Acting Injection
Ziprasidone	20mg, 40mg, 60mg, 80mg capsule			20mg/ml	
Aripiprazole	2mg, 5mg, 10mg, 15mg, 20mg, 30mg	10mg, 15mg	1mg/1ml	9.75mg/1.3ml	Abilify Maintena: 300mg, 400mg
Paliperidone	Extended Release: 3mg, 6mg, 9mg				Invega Sustenna: 78mg, 117mg, 156mg, 234mg

Antidyskinetics

- Used to treat:
  - Extrapyramidal Symptoms (EPS)
  - Relieve neurological (muscular) side effects induced by neuroleptics [Extrapyramidal Symptoms (EPS)]
  - Dyskinesia (defect in voluntary movement)
  - Dystonia (impaired/disordered tonicity, especially muscle tone)
  - Pseuoparkinsonian (tremor, rigidity)
  - Akathisia (restlessness)
  - Akinesia (muscle weakness)

Anticholinergic Medications

- Central acting medications used to restore dopamine/acetylcholine balance
- Agents
  - Benztropine (Cogentin®)→ 0.5mg-6mg/day
  - Trihexyphenidyl (Artane®)→ 5mg-15mg/day
  - Biperiden (Akineton®)→ 2mg-6mg/day
- Relieve dystonia, akathisia, pseudoparkinson, hypersalivation
- Side effects: constipation, blurred vision, dry mouth, urinary retention, nausea/vomiting

Dopamine Agonist

- Increases dopamine level at receptor site (peripherally)
- Agents
  - Amantadine (Symmetrel®)→ 100mg-300mg/day
- Similar indications as anticholinergics
- Elderly more susceptible to side-effects
  - Adjust dose for renal function
- Side effects: psychosis, nightmares, insomnia

Blocking Agents

- Possibly useful in treating EPS but most effective in treating akathisia
- Reduce adrenergic tone at central and peripheral level
- Agents
  - Propranolol (Inderal®)

Mood stabilizers

- Used to treat:
  - Bipolar Disorder
  - Mood lability

Epidemiology

- Bipolar Disorder affects 2.5 million people in the United States
- Symptoms can begin as early as 5-6 years of age
- Mean age of onset is ~18 yrs old; Symptoms may be more evident between ages 40-50 years (mid-life), but can appear at any age
- Prevalence is equal in men and women
- Genetic link: 90% have a relative with some form of depression

Bipolar Disorder

- Manic episodes alternate with episodes of depression
- Depressive and manic episodes may last several weeks to months
- Rapid cycling constitutes more than four cycles per year
- Patients often need to be managed with more than one medication

Bipolar Disorder

- Children often present with short periods of intense mood lability and irritability rather than euphoric mania
- Symptoms may be difficult to distinguish from ADHD
- ADHD often co-morbid (60-90% in pre-pubertal children; 30-40% in adolescents)
- Conduct disorder - also highly co-morbid in children and adolescents with bipolar disorder
- Bipolar II presents more often in adolescence typically with a depressive episode

Manic Symptoms

- Exaggerated optimism
- Decreased need for sleep
- Grandiose delusions; inflated sense of self importance
- Excessive irritability
- Increased goal-directed activity
- Racing/pressured speech; “flight of ideas”
- Impulsiveness, poor judgment, reckless behavior
- Easily distracted

Goals of Treatment

- Acute Stabilization
  - Relieve most severe symptoms
  - Resolve episode
  - Treat co-morbid conditions once mood is stabilized
- Continuation phase
  - 2-6 months after end of episode
  - Prevent relapse/cycling
  - Adjust mood stabilizers and taper off antipsychotics/benzodiazepines
- Maintenance

Pharmacological Treatments

- Lithium
- Anticonvulsants
- Antidepressants
- Antipsychotics
- Benzodiazepines

- Calcium channel blocking agents
  - High doses of verapamil, nifedipine, nimodipine
- Hormones
  - thyroid, estrogen/progesterone

Lithium

- Effective for manic phase and for long term maintenance
- Stabilizes mood without causing sedation (effect starts in days; 2-4 weeks for full effect)
- Exact mechanism unknown
- Not effective for rapid-cycling, but can decrease frequency of manic or depressive episodes
- May be given with an SSRI or bupropion during a depressive episode

Dosage Administration

- Initial start - 300mg bid; once a day if tolerated
- Acute Treatment: 900-2400mg/day
- Maintenance: 400-1200mg/day
- Maintain proper fluid & sodium intake
- Dose increases are based on lithium blood levels (therapeutic = 0.8-1.2) and tolerance

Lithium Side Effects

- Nausea
- Diarrhea
- Weight gain
- Polyuria
  - passing of excessive amounts of urine
- Tremor
- Hypothyroidism

Drug Interactions

- Increase Lithium Level
  - ACE inhibitors (captopril, enalapril)
  - Metronidazole
  - NSAIDS
  - thiazide diuretics; phenothiazines, haloperidol, fluoxetine - increase LI level

- Decrease Lithium Level
  - Calcium channel blockers
  - Theophylline - increase LI excretion

Carbemazepine (Tegretol ®)

- An anticonvulsant drug that may be used to treat acute mania or for prophylactic therapy
- Works well for stabilizing rapid-cycling patients
- Dosing is typically empiric
  - Initial: 100 – 200 mg/day with gradual increases in dosing weekly
  - Maximum daily dose is usually 1200 mg/day

Dosage Administration

- 200mg twice daily for 2-3 days; increase to three times daily
- Range - 300-1600mg
- Therapeutic blood level range: Css = 4 - 12 µg/ml
- Toxicity: At concentrations > 8 µg/ml patients may experience nausea, vomiting, lethargy, dizziness, drowsiness, headache, blurred vision, double vision, and ataxia. Typically seen when dosing changes are made abruptly

Carbamazepine Side Effects

- Blood dyscrasias - thrombocytopenia – decreased platelet count; leukopenia – decreased white blood cells
- Skin reactions - Stevens-Johnson Syndrome
- Low sodium blood levels - elderly highly sensitive
- Cognitive effects-sedation, gait disturbances, dizziness
- Neuromuscular effects

Carbamazepine Drug Interactions

- Increase Carbamazepine Level
  - Calcium channel blockers; cimetidine, erythromycin, valproate
- Decrease Carbamazepine Level
  - Phenobarbital
- Carbamazepine causes decreased drug effect/level
  - Oral contraceptives
  - Theophylline
  - Warfarin

Oxcarbazepine (Trileptal®)

- Mechanism of action: similar to carbamazepine
- Indications: monotherapy or adjunctive for partial seizures in adults, adjunctive therapy of partial seizures for children
- Derivative of carbamazepine
- Unlabeled uses: Acute Mania, Atypical Panic disorder

Oxcarbazepine (Trileptal®)

- Initial Dose: 150mg bid
- Maximum dose 2400mg/day in 2 divided doses
- Side effects:
  - Dose dependent: headache, drowsiness, dizziness, ataxia, tiredness, nausea
  - Idiopathic: hyponatremia, rash, weight gain
- Laboratory monitoring: not required

Valproic acid (Divalproex – Depakote®)

- Another anticonvulsant approval by FDA in 1995 for use in mania and mixed bipolar states
- Useful in rapid-cycling bipolar patients
- Dosing is typically empiric
  - Initial: 5 – 10 mg/kg/day divided three times a day
  - Increase by 5 mg/kg/day until therapeutic level/effect is achieved
- Max dose is 60 mg/kg/day

Valproic Acid Therapeutic Range/Toxicity

- Therapeutic blood level range: Css = 50 to 100 µg/ml
- Toxicity: Better tolerated than lithium but more sedating
  - > 75 µg/ml: ataxia, sedation, lethargy and fatigue which decrease with continued usage.
  - > 100 µg/ml: tremor and concentrations
  - > 175 µg/ml: stupor or coma.

Valproic acid (Divalproex – Depakote®)

- Initial start at 250mg bid then increase by 250mg every 3-4 days
- Range - 750-3000mg
- Drug Interactions:
  - Fluoxetine - increase valproic levels
  - ETOH - increase CNS depression
  - Aspirin, warfarin - increase bleeding time
  - Phenytoin - increase phenytoin levels

Lamotrigine (Lamictal®)

- Adjunct therapy to partial seizures (refractory)
- Not approved for bipolar disorder
- Inhibits release glutamate (an excitatory amino acid)
- Unlabeled uses: acute management of depression in Bipolar I and mood stabilizer in rapid-cycling Bipolar II

Lamotrigine (Lamictal®)

- Taken from seizure literature (may not be optimal for bipolar disorder)
  - 50 mg once a day for 1-2 weeks
  - Increase to 50mg twice a day for 2 weeks
  - Maintenance 300-500mg/day

- Dosage is based on enzyme inhibition and presence of valproic acid in the drug regimen
  - Consult the medication guide for more accurate dosing in these instances

Adverse Effects

Adverse Effects:

- Dizziness
- Headache
- Double vision
- Ataxia
- Nausea
- Blurred vision
- Somnolence
- Skin rash**

Mood Stabilizers

Drug Name	Tablet	Capsule	Liquid
Lithium	150mg, 300mg Controlled Release: 300mg, 450mg	150mg, 300mg	300mg/5ml
Valproic Acid & Divalproex Sodium	Depakote: 125mg, 250mg, 500mg Depakote ER: 250mg, 500mg	Valproic Acid: 250mg Depakote Sprinkle: 125mg	Valproic Acid: 250mg/5ml
Carbamazepine	Chew tabs:100mg 200mg XR tabs: 100mg, 200mg, 400mg	100mg, 200mg, 300mg extended release caps	100mg/5ml
Oxcarbazepine	150mg, 300mg, 600mg		300mg/5ml
Lamotrigine	25mg, 100mg, 150mg, 200mg Chew/dispersible tab: 2mg, 5mg, 25mg		

Resources

The following are several websites which can provide you with valuable information in performing your duties as a case manager. Please feel free to review them at your convenience:

- https://pealcenter.org/
- http://www.dhs.pa.gov/
- http://www.cms.hhs.gov/
- http://www.nami.org
- http://www.namikeystonepa.org/
- http://www.pmhca.org
- http://www.samhsa.gov/
- http://www.grants.gov/
- https://www.samhsa.gov/disorders/co-occurring

Summary

- You have completed Module 2 – Psychopharmacology for Children/Adolescents with Mental Illness.

  Please continue by completing test found on the main menu.

- Return the completed quizzes from all the modules to your supervisor. You or your supervisor will need to complete a Registration Form to send in to OERP when all your tests are completed and scored.
- Please complete an evaluation when you have completed the training at: www.surveymonkey.com/r/CM-eval

Comments

Please refer any comments or questions regarding this training to:

Doreen Barkowitz, LSW

UPMC Western Psychiatric Hospital / OERP

3811 O'Hara Street

Champion Commons Building, 3rd Floor

Pittsburgh, PA 15213

or via email to: barkowitzdh@upmc.edu

You have completed Module 2.

Please click here to return to the Main Menu.