COMMON CLINICAL ISSUES, UPDATES AND QUESTIONS ABOUT PSYCHIATRIC MEDICATIONS

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Objectives

- Review common clinical medication-related issues that arise for non-prescribing mental health clinicians in the course of treatment of their patients.
- Discuss general and specific management strategies for common drug-related issues.
- Describe recent advances in psychopharmacology.
- Respond to attendee provided questions.

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Disclosures

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Case 1

- JL is a 28 year old female recently diagnosed with major depressive disorder. She has been feeling down for several months and has recently sought treatment. She has lots of questions:
  - Why do I need to take medication?
  - Can I stop taking the medications at some point?
  - What do I do if I have side effects?
- What are some strategies for helping JL answer some of these questions?

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COMMON QUESTIONS FROM PATIENTS

- How was the drug selected?
- How did the physician arrive at the dose I am receiving?
- How was the regimen decided?
- What are the expected effects from medication?
- When will changes be made in my medication?

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COMMON QUESTIONS FROM PATIENTS

- What would happen if I took an overdose of medication?
- How long will I be treated?
- How will progress be assessed?
- What will happen if medications fail or progress is slow?
- How will I be followed for my medications? (how often, by whom, etc)

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COMMON QUESTIONS FROM PATIENTS

- When and how will the decision be made to discontinue treatment?
- How will the medication be stopped?
- What will happen after the medication is discontinued?
- Are there any things I can do other than medications to improve the outcome of treatment?
- Can I learn not to get sick again?

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IMPLICATIONS FOR MEDICATION EDUCATION

- Be aware of the common questions
- Make the patient aware of these questions
- Think about what your answers will be
- Encourage the patient to find the answers themselves
- Refer patient to another source if you cannot answer the question

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Therapeutic Effects of Psychotropic Medication

Curative versus preventative effects

- psychotropic medications relieve symptoms
- help prevent the return of symptoms
  - longer symptom free intervals between episodes
  - fewer symptoms during future episodes
  - relief of symptoms between episodes
- adjunctive therapy in the treatment of mental disorders
- not to be relied upon as sole treatment

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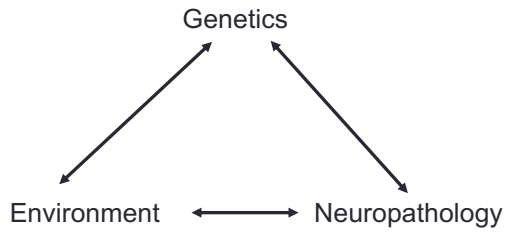
Mental Illness



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Psychotherapy

- Useful in nearly every psychiatric disorder
- Different changes in brain function
- May be imperative for response in patients with trauma history
- Generally synergistic with meds
- CBT most studied

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Therapeutic Effects of Psychotropic Medication

Onset of Effect

- Early - generally due to side effects
- Specific Effects - weeks to months

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Long-term Maintenance Treatment

1. Not necessary for all patients
2. Not predictable which patients require long-term therapy
3. Long-term therapy is used for those patients who respond and have recurrent episodes
4. First episode - 6 months
5. Consider long-term side effects in decision
6. Taper the dose to the minimal therapeutic dose
7. Consolidate of doses to improve compliance
8. Routine follow up is imperative

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Determining Need for Medication

- Based on:
  - treatment responsive symptoms
  - dangerousness
  - patient preference

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Educating to Avoid Nonadherence

- 70-80% of patients readmitted stopped taking their medication
- Medication adherence is generally poor in psychiatric patients
- Low levels of knowledge, side effects, cultural influences, high levels of knowledge, and false beliefs are some of the most popular hypotheses for nonadherence
- Inform rather than give information
- Include the family/caregiver

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Implications of Nonadherence

MEDICATION NONADHERENCE LEADS TO:

- High rate of recidivism
- Higher cost of treatment
- May potentially lead to poor prognosis
- Overall loss of functioning

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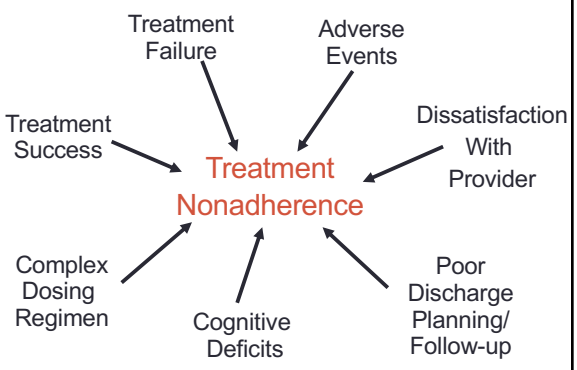

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BASIC POINTS OF INFORMATION

- type(s) of psychotropic medication(s)
- name(s) of psychotropic medication(s)
- dose patient is receiving
- purpose of medication
- common side effects of medication(s)
- what to do if side effects should happen
- signs of severe toxicity
- drug-drug and drug-food interactions
- appropriate administration

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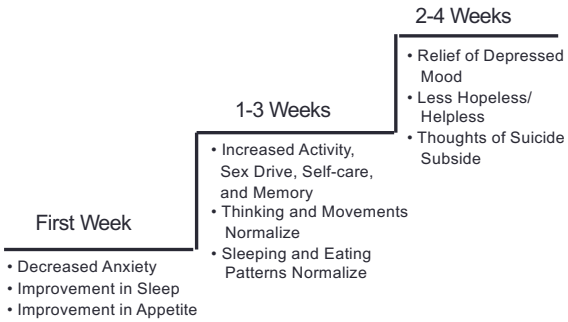
Response Model



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SIDE EFFECTS

- Limit discussion to common side effects
- Discuss patients' experience
- Discuss seeking help for side effects
- Suggestions for minimizing side effects

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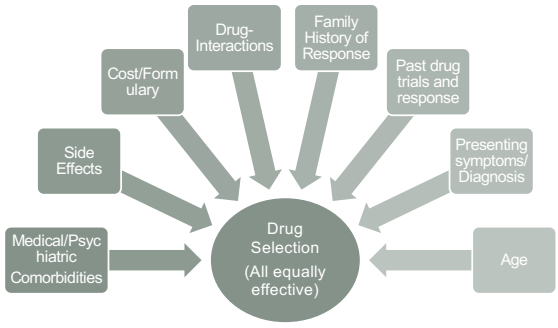
Medication Selection



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Treatment Algorithms

- Texas Medication Algorithm Project (TMAP)
- Texas Implementation of Medication Algorithm Project (TIMA)
- American Psychiatric Association (APA)
- Canadian Network for Mood and Anxiety Treatments (CANMAT)
- Expert Consensus Guidelines
- National Institute for Health and Care Excellence (NICE)

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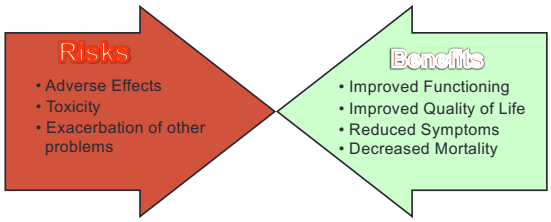
Risk: Benefit for Drug Therapy



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Generic vs. Trade Name Drugs

- Generally not a problem
- Many newer agents not yet available as generics
- Problems come when patient is switched from one to another – watch for changes in color, shape, size
- Watch for loss of therapeutic effect or emergence of side effects

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JL Continued

- JL decides to proceed with medication to manage her symptoms of depression. How can we best answer her questions about how she might respond to her medications more specifically related to the depression and potential side effects?

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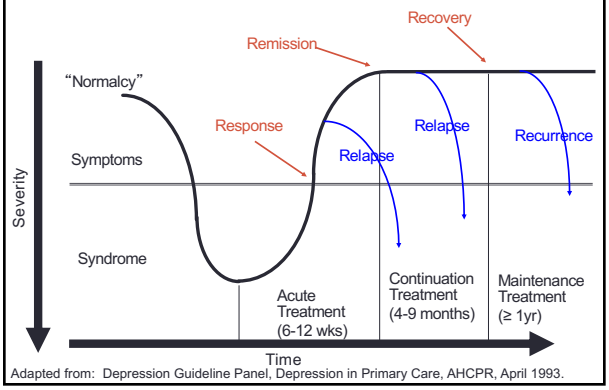
Phases of Treatment for Depression



Adapted from: Depression Guideline Panel, Depression in Primary Care, AHCPR, April 1993.

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Target Symptoms for Antidepressant Treatment

-mood/feeling
- sadness
- irritability
- pessimism
- self-reproach
- anxiety

-suicidal thoughts
-hopelessness
-guilt
-no enjoyment

-vegetative signs:
- slowed movement
- slowed thinking
- poor memory and concentration
- fatigue
- constipation
- decreased sex drive
- anorexia
- weight change
- insomnia

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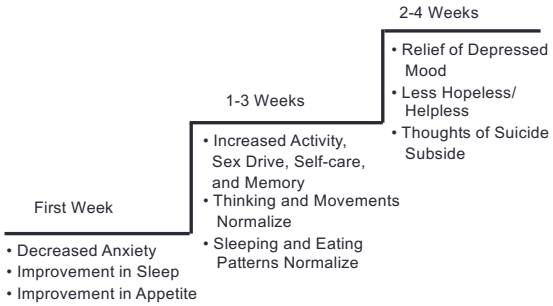
Symptom Remission



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Survival

- Recurrence rate of 30% in 3 years at full dose, 70% at half dose
- 50-70% of patients will relapse over 1 year period without maintenance treatment
- Risk of relapse continues to increase over time
- Risk of relapse significantly reduced with maintenance therapy - 80-90% remain well during first year of maintenance therapy
- Psychotherapy does not improve survival significantly over medication management

Frank, et.al., *Arch Gen Psychiatry* 1990;47:1093. Frank, et.al., *J Affect Dis* 1993;27:139. Kupfer, et.al., *Arch Gen Psychiatry* 1992;49:769

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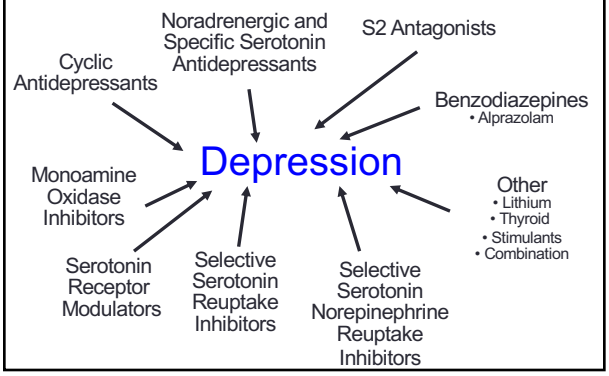
Treatment Options for Depression



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Comparative Antidepressant Pharmacology

	5-HT 1a Partial Agonist	5HT 1a Full Agonist	5HT 1b Partial Agonist	5HT 1d Antagonist	5HT 3 Antagonist	5HT 7 Antagonist	SERT Inhibitor	NET Inhibitor	NE alpha 2c	DAT Inhibitor
Tricyclics							■	■		
SSRIs							■			
SNRIs							■	■		
Bupropion								■		■
Mirtazepine									■	
Levomilnacipran							■	■		
Vilazodone	■						■			
Vortioxetine		■	■	■	■	■	■			

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Antidepressant Side Effects

SSRIs
Prozac
Zoloft
Paxil
Celexa
Lexapro

- Nausea
- Diarrhea
- Headache
- Nervousness
- Insomnia
- Sexual Dysfunction

TCAs
Elavil
Tofranil

- Drowsiness
- Dry Mouth
- Blurred Vision
- Constipation
- Hypotension
- Weight Gain
- Cardiac Effects
- Urinary Retention
- Sexual Dysfunction
- Memory Impairment

MAOIs

- Hypotension
- Dizziness
- Weight Gain
- Insomnia
- Cardiac Effects
- Constipation
- Sexual Dysfunction
- Palpitations
- Hypertensive Crisis

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Antidepressant Side Effects

SSNRI
Effexor
Cymbalta
Pristiq
Fetzima

- Nausea
- Diarrhea
- Headache
- Hypertension
- Nervousness
- Insomnia
- Sexual Dysfunction

Bupropion

- Insomnia
- Seizures
- Weight Gain
- Cardiac Effects

Trazodone

- Hypotension
- Dizziness
- Weight Gain
- Constipation
- Sexual Dysfunction
- Memory Impairment

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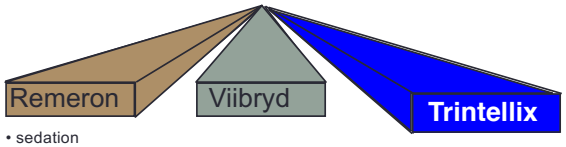
Antidepressant Side Effects



- sedation
- nausea
- weight gain
- dizziness
- dry mouth
- constipation
- visual changes
- pruitis/rash
- sexual dysfunction
- agranulocytosis

- Nausea
- Vomiting
- Diarrhea

- Nausea
- Vomiting

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Discontinuation Syndrome

- TCA withdrawal syndrome: cholinergic and/or adrenergic rebound (sweating, N/V/D)
- Serotonin withdrawal syndrome: agitation, nightmares, anxiety, dizziness, paresthesias
- Antihistaminergic withdrawal – irritability, insomnia
- Onset: 1 – 2 days after discontinuation
- Duration: 4 – 5 days
- Prevention: taper antidepressants over 2 weeks

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Suicidality Warning

- Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression is associated with an increased risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. Families and caregivers should be advised for the need for close observation and communication with the prescriber.

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Case 2

- JZ is a 42 year old African American female diagnosed with bipolar disorder. She has had multiple changes in her medication since she was first diagnosed 22 years ago. She has had multiple episodes of depression over the years and has been hospitalized twice for mania. She is wondering how the medication is helping her and why it took so long to find the right one to manage her depression.

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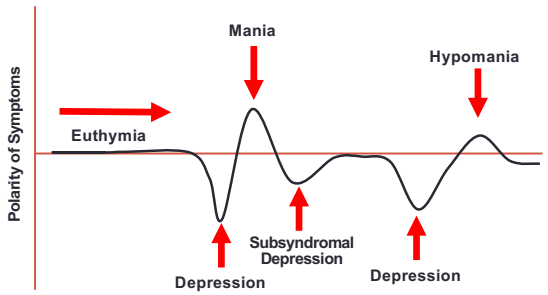
Longitudinal Assessment of Bipolar Disorder Is Critical



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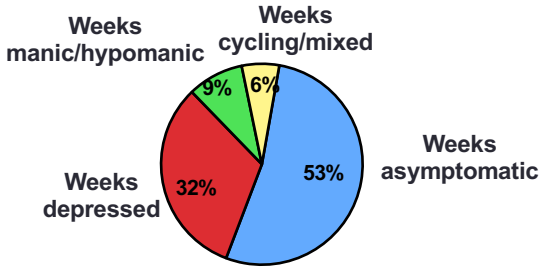
Bipolar I Patients Are Symptomatic Almost Half Their Lives



Judd et al. *Arch Gen Psychiatry*. 2002;59:530-537.

N=146
12.8-year follow-

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BIPOLAR Disorders

A. Agents and Actions

- Lithium
- Valproic acid (Depakene, Depakote)
- Carbamazepine (Tegretol, Equetro)
- Lamotrigine (Lamictal)
- Antidepressants
- Atypical Antipsychotics

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Target Symptoms for Mania

-mood disorder
- irritability
- expansive
- manipulative
- labile

-hyperactivity
- sleep disturbance
- pressured speech
- increased motor activity
- assaultive/threatening
- distractibility
- hypersexuality

-delusions
- sexual
- persecutory
- religious
- grandiose

-schizophreniform
- loose associations
- hallucinations

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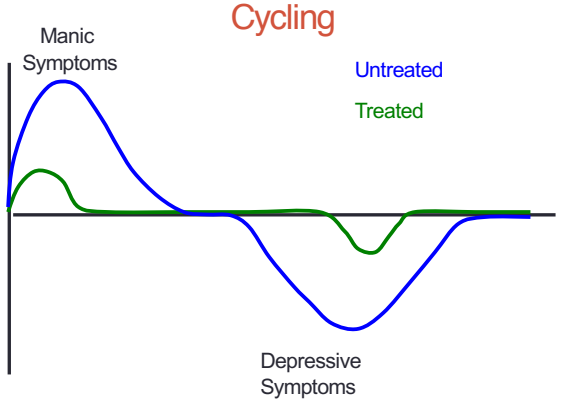
Cycling



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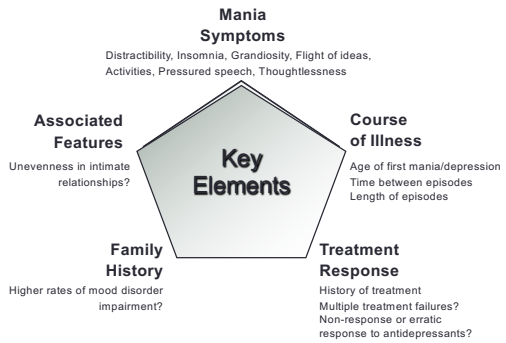
Differential Diagnosis: Unipolar or Bipolar?



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Second Generation Antipsychotics: FDA Approvals in Bipolar Disorder

Acute manic or mixed episode	Acute depressive episode	Maintenance therapy	Agitation (IM short-acting formulations only)
Olanzapine		Olanzapine	Olanzapine
Quetiapine	Quetiapine	Quetiapine, adjunct	
Risperidone		Risperidone(LAI)	
Ziprasidone		Ziprasidone, adjunct	
Aripiprazole		Aripiprazole, adjunct	
Asenapine			
	Lurasidone		
•Efficacy		Lurasidone	

–Effective in up to 70% of patients with acute mania

–Onset of effect: 3-5 days

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Lithium Toxicity and Symptoms

Mild/ Moderate 1.5-2 mEq/L	Moderate/ Severe 2-2.5 mEq/L	Severe 2.5 mEq/L
• N/V/D • Ataxia • Dysarthria • Lethargy • Coarse tremor • Nystagmus • Drowsiness	• Anorexia • Delirium • Persistent N/V/D • ECG changes • Stupor • Syncope • Myoclonus • Hyperreflexia	• Seizures • Renal failure • Oliguria • Death

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Most Common Adverse Effects

Lithium

CNS: Tremor, Sedation, Cognitive impairment
GI: Abdominal pain, Diarrhea
Other: Thirst, Polyuria, weight gain, acne

Divalproex

CNS: Tremor, Dizziness, Sedation, Headache
GI: Nausea, Abdominal pain/indigestion
Other: Weight gain

Carbamazepine

CNS: Sedation, Dizziness, Unsteady Gait, Incoordination, Blurred vision, diplopia, Cognitive impairment
GI: Abdominal pain, Diarrhea
Other: Thirst, Polyuria, weight gain, acne

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Summary Lithium

Advantages

- 80% effective for acute mania
- Most effective MS for bipolar depression
- Reduces frequency, duration and severity of future episodes

Disadvantages

- Less effective in severe mania with psychotic features, mixed, rapid-cycling, organic mania, comorbid substance abuse
- Adverse effects
- Multiple drug-drug interactions
- Blood Concentration monitoring
- Teratogenicity

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Summary Valproic acid

Advantages

- Similar efficacy to lithium for classic manic episodes
- May be more effective than lithium for mixed episodes
- May be beneficial in rapid-cycling
  - "Anti-kindling"

Disadvantages

- Adverse effects
- Multiple drug-drug interactions
- Blood Concentration monitoring
- Teratogenicity

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Summary Carbamazepine

Advantages

- Similar efficacy for classic manic episodes
- May be more effective in lithium non-responders
- May be beneficial in mixed episodes, organic mania, and rapid-cycling
  - "Anti-kindling"

Disadvantages

- Adverse effects
- Multiple drug-drug interactions
  - Auto-inducer
- Blood Concentration monitoring
- Teratogenicity

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Lamotrigine- Lamictal

Approved for maintenance

Not effective for acute manic episodes

Delayed time to intervention for depression

Less delay in time to intervention for mania

Side effects

- Headache
- Nausea
- Insomnia
- Rare 0.1% severe rash

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Miscellaneous Mood Stabilizers

- Clozapine
  - Generally 4th line agent secondary to both safety and lack of efficacy data
- Oxcarbazepine
  - Case series and a few small controlled studies suggest efficacy in bipolar disorder
- Omega III Fatty Acids
  - One RCT has found usedful for preventing the reoccurrence of symptoms
- Topiramate or Gabapentin
  - Lack of evidence supporting use in this area

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Case 3

AG is a 37 year old Caucasian female diagnosed with panic disorder. She has been treated successfully over the years on a combination of an SSRI and benzodiazepine. Lately she has been reading that many health systems are restricting the use of benzodiazepines and fears that her doctor may be forced to stop her. She fears the panic symptoms will return if that happens.

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Three Components of Anxiety

- Physical symptoms
- Cognitive component
- Behavioral component

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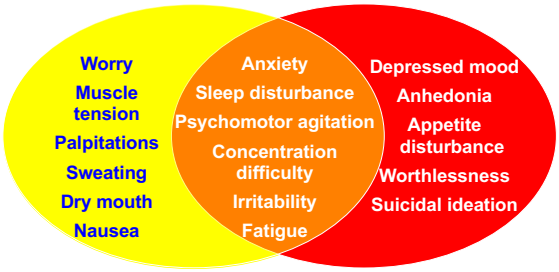
Overlapping Symptoms of MDD and GAD



DSM-5. Washington, DC: American Psychiatric Association. 2013.

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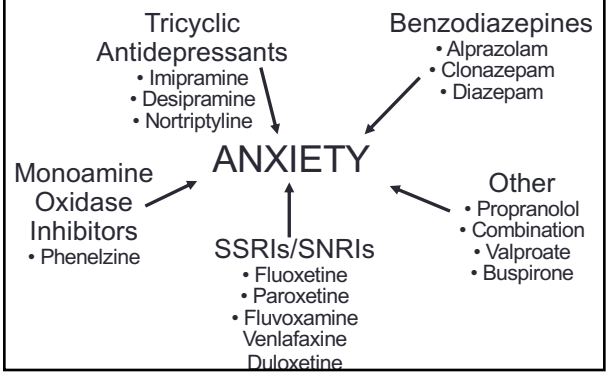
Treatment Options for Anxiety Disorders



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Antianxiety Agents

A. Agents and Actions

Benzodiazepines

- long-acting (t1/2 > 40 hours)
- medium-acting (t1/2 10-40 hours)

Non-benzodiazepine

- buspirone (BuSpar)
- meprobamate (Miltown, Equanil)

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Benzodiazepines (BZDs)

- Indications
  - Panic attacks, *not* panic disorder
  - Anxiety
  - Seizures
  - Sedatives
  - Muscle relaxants
  - Acute alcohol withdrawal
  - Acute mania
  - Acute agitation

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BZDP Agent	Dose Range(mg/d)	T1/2 (hrs)/metab	Active Metabolite
alprazolam	0.5-10	9-20	OH-alprazolam
chlordiazepoxide	5-200	4-29/28-100	DMD, oxazepam, DMC
clonazepam	0.5-6	19-60	
chlorazepate	15-60	1-120	DMD
diazepam	2-40	14-70/30-200	DMD, oxazepam, temazepam
estazolam	0.5-2.0	8-24	
flurazepam	15-30	3/40-250	N-desalkylflurazepam, OH-ethylflurazepam
halazepam	80-160	14/30-96	DMD, 3-OH-halazepam
lorazepam	2-6	8-24	
oxazepam	30-120	3-25	
prazepam	20-60	30-100	DMD, oxazepam, desalkylprazepam
quazepam	7.5-30	15-40/39-120	2-oxoquazepam, desalkylflurazepam
temazepam	15-30	3-25	
triazolam	0.125-0.5	1.5-5	7-a-OH metabolite

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Target Symptoms for Anxiety

- Motor Tension
  - Trembling, twitching or feeling shaky
  - Restlessness
  - Muscle Tension, aches or soreness
  - Easy fatigability
- Autonomic Hyperactivity
  - Shortness of breath
  - Sweating, cold clammy hands
  - Palpitations or tachycardia
  - Dry mouth
  - Dizziness or lightheadedness
  - Frequent urination/ urgency
  - Nausea, diarrhea, GI distress
  - "Lump in throat"

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Target Symptoms in Anxiety (continued)

- Vigilance and Scanning
  - Feeling keyed up or on edge
  - Easy to startle
  - Irritability
  - Insomnia
  - Difficulty concentrating
- Panic (in addition to above)
  - Choking
  - Paresthesias
  - Fear of dying
  - Fear of going crazy
  - Chest pain/discomfort

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SIDE EFFECTS

Benzodiazepine agents

- long-acting versus short-acting
- common effects

drowsiness	sedation
blurred vision	ataxia
psychomotor impairment	disorientation
aggression	confusion
excitement	

- discontinuation: rebound, relapse, recurrence and withdrawal
- abuse, dependence, addiction

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Treatment: PTSD

- Initially, trauma focused CBT and non-BZD sleep agent
- EMDR
- After 3-4 weeks of CBT and continued moderate severity of symptoms start pharmacotherapy
  - SSRI, SNRI first line
    - Start at lower dose to avoid increase in anxiety

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Treatment Considerations: PTSD

- Partial responders
  - Antipsychotic augmentation of SSRI w/ or w/o psychotic features
- Adjunct as needed for sleep, nightmares or psychotic symptoms
- Nightmares
  - Prazosin 6-10mg
    - Combat veterans may need higher doses
    - Start at 1mg, monitor BP

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Treatment Considerations: PTSD

- Propranolol, a β-adrenergic antagonist, had beneficial effects on PTSD of intrusive recollections and reactivity to traumatic stimuli
- BZDs are not effective and should be avoided due to risk of substance abuse

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Treatment: Generalized Anxiety Disorder

- SSRIs or SNRIs first-line
  - Paroxetine (Paxil), Escitalopram (Lexapro), Venlafaxine XR (Effexor XR), Duloxetine (Cymbalta) have FDA approval
- Other ADs work
- Benzodiazepines
  - Not reliable antidepressant
- Buspirone

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Treatment: Panic Disorder

SSRIs or SNRIs first-line	• Other ADs work
MAOIs	
Benzodiazepines	• Not reliable antidepressant
Beta-blockers useful adjunctive therapy	• Not adequate as monotherapy

*SNRIs are more expensive and less-well studied in PD

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Treatment: OCD

SSRI (or TCA) for 10 -12 weeks ± CBT

If inadequate response

- Taper
- Second agent for 10-12 weeks

If inadequate response

- Taper
- Third agent for 10-12 weeks
- Consider adding an augmenting agent

Treat for 1-2 years

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Case 4

- JB is a 14-year-old male diagnosed since age 10 with ADHD. His mother expresses some concerns about his medications. He has been receiving stimulant treatment since diagnosis. She has noticed that he is beginning to lose his ability to focus on his schoolwork after about 7:00 PM most nights. She is getting more notes from school that he is being disruptive in class – especially in the afternoon. He is currently taking medications twice daily. She is worried that the medications have stopped working.

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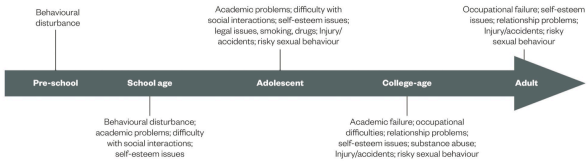
Developmental Impact of ADHD



Bhat V, Hechtman L. *Clinical Pharmacist*, February 2016, Vol 8, No 2, online | DOI: 10.1211/CP.2016.20200602

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ADHD

3 Basic Issues in Diagnosis

- Inattention - lack of detail orientation, makes mistakes, cannot sustain activity, difficulty listening, organizing, forgetful, loses things
- Hyperactivity - fidgets, moves around, difficulty being quiet, on the go, talks excessively
- Impulsivity - difficulty waiting turns, blurts out answers, interrupts/intrudes

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ADHD

ISSUES IN TREATMENT

- Education - family, child, teacher
- Parent Management Training
- School Training
- Pharmacotherapy

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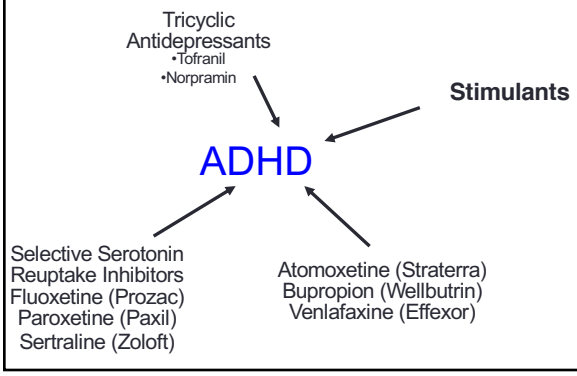
Treatment Options for ADHD



72

Target Symptoms for ADHD

73

Treatment strategies - Stimulants

- Primarily methylphenidate or amphetamine based
- Immediate release formulation –4 hours of effect
- Intermediate release – 8 hours of effect
- Extended release – 12 hours of effect
- Extensive development of creative formulations – extended release liquids, ER chewable, coatings that allow bedtime dosing

74

Pharmacokinetic/Pharmacodynamic Differences in Children and Adolescents

- Vast majority of medications are not approved for use in children and adolescents
- Differences in drug metabolism and clearance early in childhood – then adult or better levels as toddlers – declines through puberty to adult levels
- Many doses are done based on weight (mg/kg)
- Brain development is on-going for many years
- Physical development is ongoing and changing – may have different effects than adults – weight changes, sexual/hormonal effects, growth

75

ADHD Medications

TRADE NAME	GENERIC NAME	DOSAGE RANGE	MAX DOSE	DOSAGE INTERV.
Catapress	Clonidine	0.2-2.4 (mg/day)	2.4	BID-TID
Tenex	Guanfacine	0.5-3.0 (mg/day)	3.0	qd-BID
Adderall	Dextroamphetamine Amphetamine	2.5 - 40 mg/day	40	
AdderalXR, Mydayis			1/2 dose of Adderall qd/BID	
Desoxyn	Methamphetamine	5-25		
Cylert	Pemoline	0.5-3.0 (mg/kg/day)	112.5	Q AM
Dexedrine	Dextroamphetamine	0.15-0.3 (mg/kg/day)	40	BID-TID
Vivanse	Lisdexamfetamine			
Ritalin	Methylphenidate	0.3-0.6 (mg/kg/day)	60	
Ritalin, Metadate CD, Methylin ER, Ritalin LA, Cotempla XR-ODT, Jornay PM, Metadate ER&CD, QuilliChew ER, Aptensio XR, Concerta, Relexxi, Adhansia XR, ContemplaXR-ODT, Daytrana Patch, Quillivant XR				
Focalin Focalin XR	Dexmethylphenidate	1/2 Ritalin dose	20	
Dyanavel XR Evekeo ODT, Adzenys XR-ODT	Amphetamine	5-20 mg/day		
Strattera	Atomoxetine	80 mg/day	100	qd/BID
Tofranil	Imipramine	25-300 (mg/day)	300	BID-TID
Wellbutrin	Bupropion	150-450 (mg/day)	450	BID-TID
Effexor	Venlafaxine	75 - 225 (mg/day)	225	BID or qd

76

Making Sense of the Products

- The market is being driven by novel formulations to meet specific needs
  - Once daily dosing – with extended hours of coverage – from 8-16 hours
  - Convenience of dosing – available as ODT or chewable or liquid
  - Each product is slightly different from each other and they are not interchangeable for the most part
  - Brand names are significantly more expensive and often subject to prior approvals or formulary restrictions
- IR formulations need to be given more than once per day with attention paid to when the last dose is given (generally not after 4 PM)

77

SIDE EFFECTS

Stimulant Medications

- Insomnia
- Anorexia
- Weight loss
- Nausea
- Tachycardia
- Growth suppression
- Exacerbation of psychosis / mania
- Mood lability (crying)
- Irritability
- Euphoria
- Sterotypy
- Dizziness
- Tic disorders

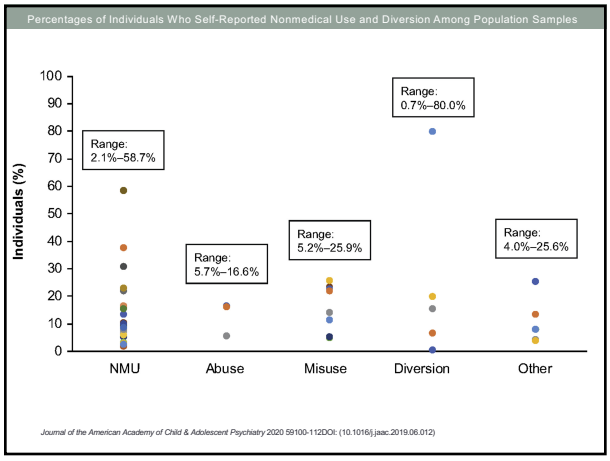
Clonidine/Guanfacine

- dry mouth
- Dizziness
- Constipation

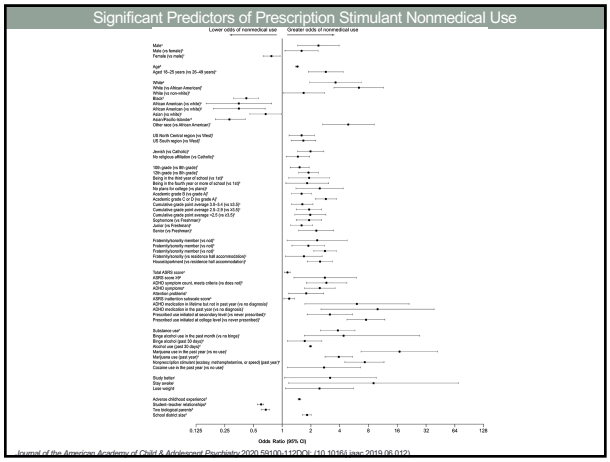
Atomoxetine

- Nausea
- Abdominal pain

78



79



80

Case 5

- QZ is a 64 year old Hispanic female. She has had episodes of anxiety and low mood for many years and has been reasonably well controlled on an antidepressant. She has recently reported difficulties with her sleeping. It takes her 90 mins to fall asleep most nights and she wakes up at 4:30 in the morning – 2 hours before she would like to awaken. This has come on in the past few months since she is approaching retirement age and she has had several friends that have had medical problems.

81

Insomnia Definition, DSM-5

A. A predominant complaint of dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings.
   3. Early-morning awakening with inability to return to sleep.

B. The sleep disturbance causes clinically significant distress or impairments in social, occupational, educational, academic, behavioral, or other important areas of functioning.

C. The sleep difficulty occurs at least 3 nights per week.

D. The sleep difficulty is present for at least 3 months.

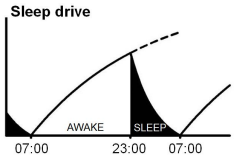
E. The sleep difficulty occurs despite adequate opportunity for sleep.

APA. *Diagnostic and Statistical Manual of Mental Disorders*. 2013.[1]

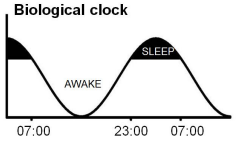
82

Physiological Control of Sleep: Two-Process Model

Homeostatic Factor (Duration of Prior Wakefulness)



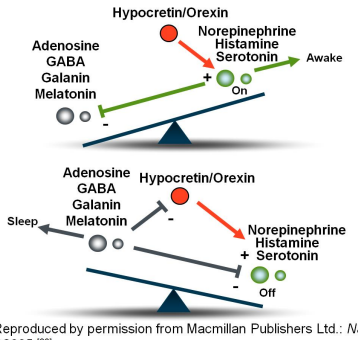
Circadian Factor (Biological Clock)



Borbély, AA. *Hum Neurobiol*. 1982;1:195-204.[18]

83

Sleep/Wake Reflects Balance Between Opposing Systems



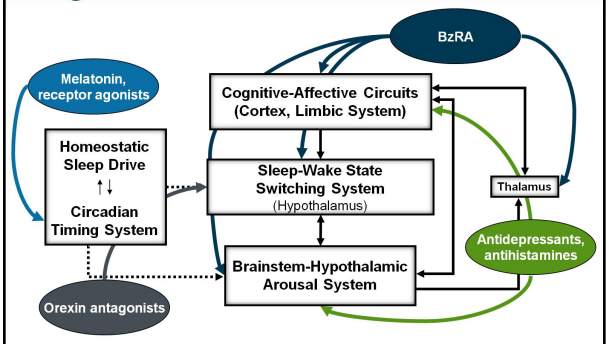
Waking: Balance is shifted toward greater activity in wake-promoting systems

Sleep: Balance is shifted toward greater activity in sleep-promoting systems

Reproduced by permission from Macmillan Publishers Ltd.: *Nature*. 2005;437:1257-1263., ©2005.[20]

84

Conceptual Model of Sleep/Wake Regulation Relevant to Insomnia



Buysse DJ, et al. *Drug Discov Today Dis Models*. 2011;8:129-137.[19]

85

SLEEP HYGIENE

- Avoid alcohol, nicotine, caffeine, chocolate, fluids
  - For several hours before bedtime
- Cut down on non-sleeping time in bed
  - Bed only for sleep and satisfying sex
  - do not read, watch tv, or study in bed - learn to associate your bed with relaxation
- Avoid trying to sleep
  - You can't make yourself sleep, but you can set the stage for sleep to occur naturally
- Avoid a visible bedroom clock with a lighted dial
  - Don't let yourself repeatedly check the time!
  - Can turn the clock around or put it under the bed

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SLEEP HYGIENE

- Avoid vigorous exercise before sleep
- Avoid late afternoon or evening naps
- Avoid eating large meals before bed
- Do not allow yourself to lie in bed and worry
  - get up and do something to alleviate the worry (like journaling)
- Take a warm bath before bed if you have a particularly difficult time getting to sleep

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SLEEP HYGIENE

- Establish a regular sleep schedule
  - Get up at the same time 7 days a week
  - Go to bed at the same time each night
- Exercise every day - exercise improves sleep!
- Deal with your worries before bedtime
  - Plan for the next day before bedtime
  - Set a worry time earlier in the evening
- Avoid oversleeping or lying in bed for prolonged periods of time after your sleep is completed

88

SLEEP HYGIENE

- Adjust the bedroom environment
  - Sleep is better in a cool room, around 65 F.
  - Darker is better
  - If you get up during the night to use the bathroom, use minimum light
  - Use a white noise machine or a fan to drown out other sounds
  - Make sure your bed and pillow are comfortable
  - If you have a partner who snores, kicks, etc., you may have to move to another bed (try white noise first)

89

Classes of Pharmacologic Agents Used to Treat Insomnia

- Benzodiazepine receptor agonists
  - True benzodiazepines
  - "Nonbenzodiazepines"
- Melatonin and melatonin receptor agonists
- Sedating "antidepressants"
- Antihistamines
- Natural agents
- Sedating second-generation antipsychotics
- Miscellaneous

Schutte-Rodin S, et al. *J Clin Sleep Med*. 2008;4:487-504.[17]

90

Medications Used to Treat Sleep Disorders

Trade Active Name	Generic Name	Control Drug Sched.	t1/2 hr	Dose	Sedative of Txt.	Length Metab
Benadryl®	diphenhydramine	No	2-8	25-50	n/a	-
Desyrel	trazodone	No	8	25-100	n/a	Yes
Sinequan	doxepin	No	6-8	10-25	n/a	Yes
Silenor	doxepin	No	6-8	3-6	up to 4wks	Yes
Noctec®	chloral hydrate	C-IV	8-11	250-2000	2-3d	Yes
Dalmane®	flurazepam	C-IV	>100	15-60	n/a	Yes
Doral®	quazepam	C-IV	>100	7.5-015	n/a	Yes
Halcion®	triazolam	C-IV	2	0.125-0.5	n/a	No
ProSom®	estazolam	C-IV	10-24	1-2	n/a	No
Restoril®	temazepam	C-IV	10-40	15-30	n/a	No
Ambien®	zolpidem	C-IV	2-2.6	5-20	5-10d	No
Sonata ®	Zaleplon	C-IV	1-2	5-20	5-10d	No
Lunesta	Eszopiclone	C-IV	6	1-3 mg	up to 6 mo	Yes
Belsomra	Suvorexant	C-IV	12	5-20 mg	3 mo	No
Rozerem	ramelteon	no		8 mg	21	No

91

Case 6

- NF is a 28 year old African American male diagnosed with schizophrenia approximately 5 years ago. He has had multiple hospitalizations in that time and has been on 3 different oral antipsychotics. His mother is concerned that he will continue down this path of rehospitalization and medication switches. He is being considered for placement with an ACT Team. She wonders what can be done with his medications. She also says that he moves around a lot and wonders if it could be his medications causing it.

92

Characteristics of Second-Generation Antipsychotics

Characteristic	CLZ	RIS	OLZ	QUE	ZIP	ARI	PALI	ILO	ASE	LUR	CAR	LUM
Little or no EPS	Y	Y/N	Y	Y	Y	Y	Y/N	Y	Y	Y	Y	Y
Efficacy for negative symptoms	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Absence of TD	Y	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Lack of effect on prolactin levels	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
DA/5HT mechanism	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Superior efficacy	Y	N	N	N	N	N	N	N	N	N	N	N

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Adverse Effects of Antipsychotics

Sedation – tolerance usually develops in 2 weeks

Anticholinergic side effects: tolerance usually develops to these side effects over 1-2 months.

-dry mouth
-blurred vision
-constipation
-urinary retention
-nasal congestion
-increase in heart rate
-**decreased sweating**

Cardiovascular side effects

-postural hypotension
-arrhythmias/palpitations

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ANTIPSYCHOTIC SIDE EFFECT PROFILE

Drug	EPS	TD	Prolactin	Weight Gain	Lipid Increase	Glucose Intol	Antichol	Sedation	CV
High Potency Conventional AP	+++	+++	+++	+	+	+	++	++	++
Low Potency Conventional AP	++	++	++	++	+	+	+++	+++	+++
Clozapine	+/-	+/-	+	+++	++	++	++	+++	+++
Risperidone	++	+	++	+	+	+	+	+	+
Olanzapine	+	+	+	+++	++	++	+	++	++
Quetiapine	+	+	+	++	++	++	++	++	++
Ziprasidone	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Aripiprazole	+	+	0	+/-	+/-	+/-	+/-	+/-	+
Paliperidone	++	+	++	+	+	+	+	+	+
Asenapine	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Lurasidone	+	+	+	+/-	+/-	+/-	+/-	+	+
Brexpiprazole	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Cariprazine	+-++	+	0	+/-	+/-	+/-	+/-	+/-	+
Lumeteperone	+/-	+	0	+/-	+/-	+/-	+/-	+/-	+/-

+++ substantial risk, ++ moderate risk, + mild risk, +/- minimal risk or insufficient data

Mueser KT, Jeste DV., in Clinical Handbook of Schizophrenia, 2008, Fuller M, Sajatovic M, in Psychotropic Drug Information Handbook 2009, Drug Pts

95

ANTIPSYCHOTIC SIDE EFFECT PROFILE

Drug	EPS	TD	Prolactin	Weight Gain	Lipid Increase	Glucose Intol	Antichol	Sedation	CV
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Low Potency Conventional AP	++	++	++	++	+	+	+++	+++	+++
Clozapine	+/-	+/-	+	+++	++	++	++	+++	+++
Risperidone	++	+	++	+	+	+	+	+	+
Olanzapine	+	+	+	+++	++	++	+	++	++
Quetiapine	+	+	+	++	++	++	++	++	++
Ziprasidone	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Aripiprazole	+	+	0	+/-	+/-	+/-	+/-	+/-	+
Paliperidone	++	+	++	+	+	+	+	+	+
Asenapine	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Lurasidone	+	+	+	+/-	+/-	+/-	+/-	+	+
Brexpiprazole	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Cariprazine	+-++	+	0	+/-	+/-	+/-	+/-	+/-	+
Lumateperone	+/-	+	0	+/-	+/-	+/-	+/-	+/-	+/-

+++ substantial risk, ++ moderate risk, + mild risk, +/- minimal risk or insufficient data

Mueser KT, Jeste DV., in Clinical Handbook of Schizophrenia, 2008, Fuller M, Sajatovic M, in Psychotropic Drug Information Handbook 2009, Drug Pts

96

ANTIPSYCHOTIC SIDE EFFECT PROFILE

Drug	EPS	TD	Prolactin	Weight Gain	Lipid Increase	Glucose Intol	Antichol	Sedation	CV
High Potency Conventional AP	+++	+++	+++	+	+	+	++	++	++
Low Potency Conventional AP	++	++	++	++	+	+	+++	+++	+++
Clozapine	+/-	+/-	+	+++	++	++	++	+++	+++
Risperidone	++	+	++	+	+	+	+	+	+
Olanzapine	+	+	+	+++	++	++	+	++	++
Quetiapine	+	+	+	++	++	++	++	++	++
Ziprasidone	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Aripiprazole	+	+	0	+/-	+/-	+/-	+/-	+/-	+
Paliperidone	++	+	++	+	+	+	+	+	+
Asenapine	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Lurasidone	+	+	+	+/-	+/-	+/-	+/-	+	+
Brexpiprazole	+	+	+	+/-	+/-	+/-	+/-	+/-	+
Cariprazine	+-++	+	0	+/-	+/-	+/-	+/-	+/-	+
Lumateperone	+/-	+	0	+/-	+/-	+/-	+/-	+/-	+/-

+++ substantial risk, ++ moderate risk, + mild risk, +/- minimal risk or insufficient data

Mueser KT, Jeste DV., in Clinical Handbook of Schizophrenia, 2008. Fuller M, Sajatovic M, in Psychotropic Drug Information Handbook 2009. Drug Pls

97

Extrapyramidal Side Effects

- Neurological side effects most troublesome
- Risk greater with first generation antipsychotics
- Can contribute to non-compliance
- Four major classifications
  - Pseudoparkinsonism
  - Dystonia
  - Akathisia
  - Tardive Dyskinesia

Practice Guideline for the Treatment of Patients with Schizophrenia. American Psychiatric Association 2010.
Kane JM. Journal of Clinical Psychiatry 2004; 65 (suppl 9):16-20.

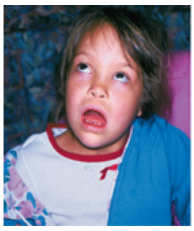
98

Acute Dystonia

Onset	• ≤5 days of treatment initiation or dose increase
Symptoms	• Severe muscle spasm of eyes, tongue, pharynx or larynx, back, neck
Risk Factors	• Young, African American males • High AP potency/doses, IM administration
Treatment	• Acute treatment → Anti-ACh agent or BZD • Chronic treatment → Decrease dose, change AP, Anticholinergic agent

99

Acute Dystonia



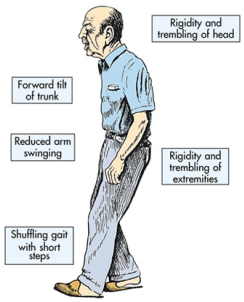
100

Pseudoparkinsonism

Onset	• ≤ 1-3 months of treatment initiation or dose increase
Symptoms	• Bradykinesia, tremor, drooling, cogwheel rigidity, postural abnormalities
Risk Factors	• >40 yo, female, high AP potency/doses
Monitoring	• Modified Simpson Angus Scale (MSAS)
Treatment	• Decrease dose, change AP, Anticholinergic agent, DA agonist

101

EPS - Pseudoparkinsonism



102

Akathisia

Onset	• ≤ 1-4 weeks of treatment initiation or dose increase
Symptoms	• Extreme motor restlessness/inability to sit still • Difficult to distinguish from anxiety/agitation/psychosis
Risk Factors	• Young, high AP doses, other meds • Up to 30% incidence with high potency FGAs
Monitoring	• Barnes Akathisia Scale (BAS)
Treatment	• Decrease dose, change AP, beta-blocker, BZD • Anticholinergic agents are ineffective!

103

Tardive Dyskinesia

Onset	• Typically later in treatment (months-years)
Symptoms	• Buccal-lingual-masticatory (BLM) syndrome, orofacial movements, writhing movements of face, neck, back, trunk and extremities
Risk Factors	• Increased age, female, concurrent diagnosis of mood disorder, long duration of AP use
Monitoring	• AIMS or DISCUS every 6-12 months
Treatment	• *Prevention* • Decrease dose of AP or switch from FGA → SGA/clozapine

104

Medications Used to Treat EPS and Dosage Ranges

			DOSE (mg)		
TRADE NAME	GENERIC NAME	T1/2	DYSTONIA	PSEUDO PARKINSON	AKATHISIA
Akineton®	biperiden	-	-	4-20	-
Artane®	trihexyphenidyl	3-4	-	4-20	-
Ativan®	lorazepam*	10-20	0.5-2 IM	-	0.5-10
Benadryl®	diphenhydramine*	2-8	25-50 IM	50-200	-
Cogentin®	benztropine*	6-48	1-2 IM	4-10	-
Inderal®	propranolol	4-6	-	-	90-160
Symmetrel®	amantadine	10-28	-	100-400	-

* - available in intramuscular dosage form

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Valbenazine (Ingrezza)

- VMAT2 reversible inhibitor
- Valbenazine is structurally related to tetrabenazine
  - Converted to [+]-α-dihydrotetrabenazine (DTBZ)
  - Once daily dosing
- FDA approved for tardive dyskinesia
- Uses Specialty Pharmacy for distribution

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Deutetrabenazine (Austedo)

- VMAT2 reversible inhibitor
- Deutetrabenazine is structurally related to tetrabenazine
  - Substitutes deuterium for hydrogen
  - 2-fold increase in systemic exposure to total (α+β)-HTBZ, a near doubling of half-life and minor increases in C_{max}
  - Allow for lower doses to be used
  - BID dosing
- FDA approved for tardive dyskinesia and Huntington's Disease – Boxed Warning
- Uses Specialty Pharmacy for distribution

Huntington Study Group. *JAMA*. 2016; Stamler D, et al. *Neurology*. 2013.

107

Metabolic Side Effects of SGAs

Drug	Weight Gain	Risk for Diabetes	Worsening of Lipid Profile
Clozapine	+++	++	+
Olanzapine	+++	++	+
Quetiapine	++	+	+
Risperidone	++	+/-	+/-
Paliperidone*	++	+/-	+/-
Asenapine*	++	+/-	-
Ziprasidone	+/-	+/-	-
Aripiprazole	+/-	+/-	-
Iloperidone*	+/-	+/-	-
Lurasidone*	+/-	+/-	-
Brexpiprazole*	+/-	+/-	-
Cariprazine*	+/-	+/-	-
Lumateperone*	+/-	+/-	-

(+) = increase effect; (-) = no effect;
*Newer drugs with limited long-term data

***Diabetes Care* 2004; 27(2):596-601, Product Pls.**

108

Atypicals - Adverse Effects

Clozapine (Clozaril)	• Weight Gain, Sedation, Orthostasis, Hypersalivation, Constipation, Seizures, WBC
Risperidone (Risperdal)	• EPS, Sedation, Akathisia
Olanzapine (Zyprexa)	• Weight Gain, Sedation, Akathisia, Orthostasis, Akathisia
Quetiapine (Seroquel)	• Anticholinergic, Sedation, Orthostasis
Ziprasidone (Geodon)	• Insomnia, Sedation
Aripiprazole (Abilify)	• Insomnia, Nausea, Akathisia
Paliperidone (Invega)	• Sedation, EPS, Akathisia
Lurasidone (Latuda)	• Insomnia, Nausea, Akathisia
Brexpiprazole (Rexulti)	• Insomnia, Nausea, Akathisia
Cariprazine (Vrylar)	• Insomnia, Nausea, Akathisia
Lumateperone (Caplyta)	• Sedation

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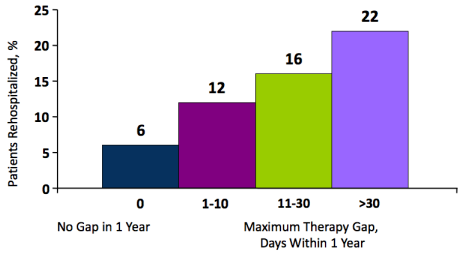
Clozapine: Black Box Warnings

Agranulocytosis	• CBC monitoring (weekly – monthly) • Goal WBC > 3.5 and ANC > 2
Orthostatic Hypotension, Syncope, Bradycardia	• Slow dose titration • Restart titration if > 2 days missed
Seizures	• Dose related (>600 mg/d)
Myocarditis	• Especially within first 8 weeks • Assess for dyspnea, fatigue, palpitations, fever, chest pain, heart failure, ECG findings, tachypnea

110

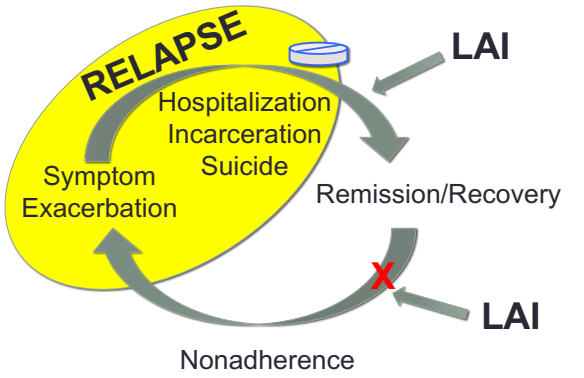
Effect of Medication Gap on Subsequent Rate of Rehospitalization in Predominantly *Adherent* Patients



Adapted from Weiden PJ, et al. *Psychiatr Serv.* 2004.

111

The Nonadherence-Relapse Cycle



112

Potential Advantages of Long-Acting Injectable Antipsychotics

- Predictable and consistent drug delivery
  - Eliminates first pass and bioavailability differences
  - Better dose to concentration predictability
- Easier to assess adherence/nonadherence
- Covert nonadherence is avoided
- Reduce risk of overdose by patient
- More convenient to patient – may be preferable to patient

NICE Guidelines for Schizophrenia. 2009, McEvoy JP. *J Clin Psychiatry.* 2006

113

New Medications – recent and pipeline agents

114

Esketamine (Spravato)

- Nasal inhaler formulation of esketamine – one of the enantiomers of ketamine
- Strict utilization guidelines for clinical use, including a waiting period after the inhaler is given
- Shows good results in rapid response of depression symptoms – and can use for longer periods of time
- Easier to use versus IV ketamine
- More expensive??
- Major side effect is disassociation

115

Lumateperone (Caplyta)

- Recently approved for treating schizophrenia
- Is a potent antagonistic serotonin 2A (5-HT2A) receptors and also binds to dopamine (D1, D2) receptors with partial agonism at presynaptic D2 receptors and postsynaptic antagonism. Also has SSRI and glutamate activity.
- Efficacy in reducing psychosis is similar to others in the class
- Safety profile – very limited increases in metabolic, EPS primary side effect is sedation (mild)
- Only has a 42 mg dose

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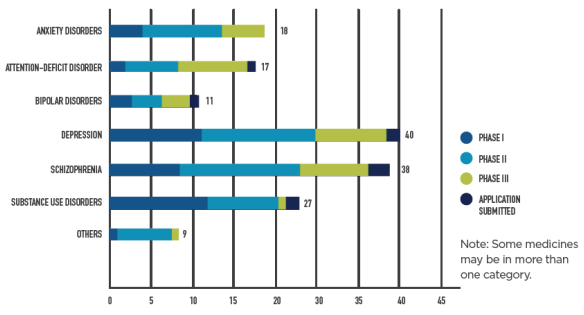
Psychopharmacology Pipeline



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Depression Pipeline

- Sage-217 – GABA receptor modulator with potentially a fast onset of antidepressant action
- R-Ketamine and Hydroxynorketamine – the other enantiomer and the metabolite of Ketamine – have somewhat different pharmacology and potency and may not cause the dissociative side effects
- LY03005 – ansofaxine – serotonin-norepinephrine-dopamine triple re-uptake inhibitor. NDA filed. Potential for less sexual dysfunction?
- AXS-05 – dextropethorphan + bupropion – potential to capture some glutamate activity
- Samidorphan – opiate antagonist – failed initial studies – showed good response

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Psychosis Pipeline

- SEP-363856 – TAAR1 and 5HT1a agonist – granted breakthrough status for schizophrenia
- ALKS 3831 - Salmidorphan/Olanzapine – opiate antagonist in combination with an SGA. Mitigates the metabolic effects of OLZ, may have specific effects on mood, SUDs
- Continued potential for additional LAIs – including risperidone and lumateperone and formulations that extend the dosing intervals to 6-12 months

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Others

- Dasotraline – serotonin, NE and DA reuptake inhibitor, metabolite of sertraline (Zoloft), in development in BED, Bipolar disorder, ADHD
- Agomelatine – Melatonin and serotonin active agent in development for anxiety and depression
- Multiple other formulations of stimulants for ADHD
- Several opiate active agents for treating SUD

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