Drug Therapy Management Series: Psychiatric Disorders

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Darrell has published over 70 papers in the medical and pharmacy literature, has lectured extensively both locally and nationally and has served as an investigator in several clinical trials. He has made numerous appearances on local television and radio programs. He also serves on several national advisory panels and is an author for WebMD’s Medscape.com and a speaker and author for AMN Healthcare's RxSchool.com.

Darrell currently practices as a clinical pharmacist with University Hospitals, Case Medical Center, Family Medicine Residency Program, where he works in consultation with family physicians, both on inpatient and outpatient services. Darrell has been the recipient of multiple teaching awards. He also completed a federal, multi-agency faculty development fellowship to further his expertise in the field of addiction medicine. He also served as a co-investigator for a multidisciplinary chronic pain study funded by the Macy Foundation. He was recently awarded a federal grant as a co-investigator to develop leadership and advocacy in urban health and community health within a multidisciplinary team.
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Purpose
This course aims to improve APRNs’ understanding of the epidemiology, clinical features, and therapeutic management of common mood and anxiety disorders, and the impact of poor medication adherence. The course also includes a discussion of strategies that can be employed to improve medication adherence in patients with common chronic psychiatric disorders.

Learning Objectives
At the conclusion of this continuing education lesson, the APRN will be able to:

1. Describe the epidemiology and clinical presentation of unipolar depression, bipolar disorder, and panic disorder.
2. Summarize effective non-pharmacological treatment options for unipolar depression, bipolar disorder, and panic disorder.
3. List underlying medical conditions, physiologic causes, and substances that can precipitate panic attacks and exacerbate depression or mania.
4. Differentiate the major classes of medications used to treat depression, bipolar disease, and panic disorder with respect to their pharmacological profile.
5. Describe the socioeconomic impact of medication non-adherence.
6. Discuss strategies that nurses can implement to improve medication adherence in patients with psychiatric disorders.

Unipolar Depression

Epidemiology of Depression ¹-⁵

- In any given year ~14.8 million Americans adults experience a major depressive episode.
- The overall lifetime prevalence of depression in women is 10-25% and 5-12% in men.
- The point prevalence of major depressive disorder in the US is 5.4-8.9%, but has been reported as high as 16.2%.
- Elderly individuals are more likely to experience major depression, relative to those younger.
- The prevalence in adults aged 65-80 years is 20.4% in women and 9.6% in men.
Epidemiology of Depression

- First-degree relatives of patients with depression are 1.5-3 times more likely to develop depression.
- For example, ~8-18% of patients with major depression have at least one first-degree relative with a history of depression.
- Major depressive disorder can develop at any age, however, the median age at onset is 32 years.
- Up to 15% of depressed patients attempt suicide.
- More than 22% of female high school students and over 11% of male high school students reported one current or lifetime episode of unipolar depression.
- A person with depression without fluctuating periods of mania or hypomania (defined later) has unipolar depression, also known as depressive disorder.

Test Yourself

Major depressive disorder can develop at any age, however, the median age at onset is:
- A. 12 years
- B. 32 years
- C. 55 years
- D. 70 years

The answer is B: 32 years.

The Socioeconomic Impact of Depression

<table>
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<tr>
<th>Socioeconomic Costs</th>
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<tbody>
<tr>
<td>Total costs</td>
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<tr>
<td>Direct costs</td>
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<tr>
<td>Indirect costs</td>
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</tbody>
</table>

Significantly greater utilization of healthcare resources, greater LOS, etc. compared to controls.
DSM-V
According to the 5th Edition (DSM-V) manual, the following diagnostic criteria can be used to confirm a diagnosis of depression.

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   1. Depressed mood most of the day nearly every day.
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day.
   3. Significant weight loss when not dieting or weight gain.
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day.
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or guilt nearly every day.
   8. Diminished ability to think or concentrate, or indecisiveness.
   9. Recurrent thoughts of death or suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiologic effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

D. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), the symptoms persist for longer than two months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.
Symptoms of Depression: SIGECAPS

Eight of the nine symptoms of depression can be easily remembered using the SIGECAPS acronym:

- Suicidal thoughts
- Interest (loss of interest in activities, anhedonia)
- Guilt feelings
- Energy decline
- Concentration problems
- Appetite changes
- Psychomotor changes (slow movement and lack of facial expression)
- Sleep disturbances

**Dysthymia or Dysthymic Disorder**

Dysthymia or dysthymic disorder is marked by depressed mood for at least two years. Depression is present for most of the day, for more days than not. The depressed mood is accompanied by two or more of the following symptoms:

- Decreased or increased appetite
- Insomnia or hypersomnia
- Low energy
- Poor self esteem
- Poor concentration
- Hopelessness

Symptoms are not as numerous as in major depression. Symptom free periods during the course of dysthymia can occur.

**Other Depressive Disorder**

Unipolar depression, major depression, or major depressive episode (MDE) is the focus of this module. However, many depression subtypes exist such as:

- Seasonal affective disorder
- Depression with melancholic features
- Depression with catatonic features
- Atypical depression
- Depression with psychotic features
- Postpartum depression
Co-Morbid Conditions Associated with Depression \textsuperscript{8,9,10}

- 25% of patients with Alzheimer’s disease have depression.
- 46% of patients with Parkinson’s disease have depression.
- Up to 60% of all stroke patients suffer from depression.
- Depression can also be experienced in association with:
  - Primary sleep disorder (insomnia, Obstructive Sleep Apnea)
  - Endocrine disorder (hyperthyroidism, Cushing’s disease)
  - Nutritional deficiencies (vitamin B complex)
  - Chronic pain syndromes (fibromyalgia)
  - Malignancy
  - Neurological (Multiple Sclerosis)
  - Substance use disorders (cocaine and stimulant withdrawal)

Test Yourself
Co-morbid conditions associated with depression include:

A. Alzheimer’s disease
B. Parkinson’s disease
C. Stroke
D. All of the above

The answer is D: All of the above.

Medications Associated with Depression \textsuperscript{2,11}
The following groups of medications can contribute to the development of depression:

- Centrally-acting antihypertensives (clonidine, reserpine, methyldopa, beta-blockers)
- Varenicline
- Hormonal therapy (estrogens, corticosteroids)
- Interferon
- CNS depressants and opiates
- Tamoxifen
- Certain anticonvulsants (e.g. levetiracetam, topiramate, vigabatrin)

Etiology and Pathogenesis of Depression \textsuperscript{2,6,12}
The cause of depression is too complex to be explained by a single sociological, developmental, or biological theory. The pathogenesis is perhaps better viewed as being multifactorial, involving a genetic predisposition, as well as psychosocial, environmental, and biological factors.
Several theories postulated to explain its pathophysiology:
  - Biogenic Amine Hypothesis
  - Postsynaptic Changes in Receptor Sensitivity
  - Dysregulation Hypothesis
  - Serotonin-Norepinephrine Link Hypothesis
  - Dopamine Theory

### Pathophysiology of Depression\(^{12,13}\)

The following neuronal and/or hormonal deficiencies have been proposed as contributing to depression:

- Serotonin (SER)
- Norepinephrine (NE)
- Dopamine (DA)
- Gamma aminobutyric acid (GABA)
- Brain-derived neurotrophic factor
- Somatostatin
- Thyroid-related hormones

### Pathophysiology of Depression\(^{12,13}\)

No single unifying theory can explain the pathophysiology of major depressive disorder. However, the influence of genetic factors in the development of depression is estimated at 40%. Other than genetics, a number of other factors contribute to the development and or exacerbation of major depressive disorder, including:

- Childhood trauma
- Recent stress
- Interpersonal adversity
- Lifetime trauma
- Low social support
- Concurrent medical and/or psychiatric illnesses

### Test Yourself

The norepinephrine dysregulation hypothesis is considered the single unifying theory to explain the pathophysiology of depression.

A. True  
B. False

**The answer is B: False.**

### Screening for Depression\(^{14}\)

The following two question test can be used to screen for depressed mood and anhedonia (loss of interest or pleasure in most or all activities):

1. During the past month, have you been bothered by feeling down, depressed, or hopeless?  
2. During the past month, have you been bothered by little interest or pleasure in doing things?
A variety of more detailed screening instruments are used to screen for depression and monitor a patient’s clinical response to treatment. Examples include the following:

- Beck Inventory (BI)
- Hamilton Depression Rating Scale (HDRS)
- Patient Health Questionnaire (PHQ-9)
- Geriatric Depression Scale (GDS)

Supportive Therapy for Depression

- Nondrug treatment, such as counseling and behavioral therapy is considered the cornerstone of treatment by many experts.
- A combination of psychotherapy plus medication is needed for most patients.
- Examples of nonpharmacological therapy:
  - Cognitive-behavioral therapy
  - Interpersonal therapy
  - Psychoanalysis
  - Family therapy
  - Insight training
  - Light therapy
  - Electroconvulsive therapy

Pharmacotherapy for Depression

Factors to consider when choosing an antidepressant:

- Patient preference
- Patient's history of prior response to medication
- Relative efficacy and effectiveness
- Safety, tolerability, and anticipated side effects
- Patient's concurrent medical and psychiatric history
- Presenting symptoms (psychomotor features)
- Potential for drug interactions
- Pharmacokinetics and drug half-life
- Drug cost, formulary concerns
Pharmacotherapy for Depression Clinical Pearls $^{17,18}$

- No reliable biological, genetic, or clinical predictors exist to help choose between antidepressants and psychotherapy, or to make a selection among specific antidepressants or psychotherapies.
- As with many other drug therapy decisions, systematic follow-up, assessment, and adjustment of treatment are more important than initial treatment choices.
- A recent meta-analysis supports the superiority of antidepressants plus psychotherapy, versus psychotherapy alone for the initial treatment of mild to moderate major depression.

Test Yourself

Factors to consider when choosing an antidepressant medication include:

A. Patient's concurrent medical and psychiatric history
B. Presenting symptoms
C. Potential for drug interactions
D. All of the above

The answer is D: All of the above.

Overview of Tricyclic Antidepressants (TCAs) $^{2,13,16,19,20}$

Amitriptyline, Doxepin, Imipramine, Trimipramine, Desipramine, Nortriptyline, Protriptyline, Clomipramine

- TCAs work by increasing concentration of sertraline (SER) and/or SER in the CNS and may also possess affinity for muscarinic and histamine H1 receptors.
- The initial dose is 10-25 mg/day of desipramine equivalent, with a range of 100-300 mg/day.
- Adverse drug reactions include weight gain, blurry vision, fatigue, constipation, headache, somnolence, dizziness, cardiac arrhythmia, liver enzyme changes, QT prolongation.

Did You Know?

Black Box Warning (BBW): Antidepressants increase risk of suicidal thoughts in children, teens, and young adults.
Overview of Tricyclic Antidepressants (TCAs) $^{2,13,16,19,20}$

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Gen. Avail.</th>
<th>Mechanism of Action</th>
<th>Dosing</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sinequan</td>
<td>Doxepin</td>
<td>Yes</td>
<td>Increases the synaptic concentration of serotonin and norepinephrine in the central nervous system</td>
<td>Initial: 25 mg/day, Range: 100-300 mg/day Dosage reduction required in elderly patients</td>
<td>Weight gain, constipation, blurred vision, dry mouth, dizziness, somnolence, libido changes, QT prolongation, photosensitivity</td>
<td>BBW: Antidepressants increase risk of suicidal thoughts in children &lt;12, adolescents, and young adults (18-24 y.o.) BBW: Not FDA approved for treatment of Bipolar Disorder Depression</td>
</tr>
<tr>
<td>Tofranil</td>
<td>Imipramine</td>
<td>Yes</td>
<td>Increase the synaptic concentration of serotonin and/or norepinephrine in the CNS</td>
<td>Initial: 25 mg/day, Range: 100-300 mg/day Dosage reduction required in elderly patients</td>
<td>Weight gain, bloating, symptoms, dry mouth, dizziness, headache, asthenia, urinary retention, blurred vision, fatigue, QT prolongation, angioedema, sexual dysfunction</td>
<td>BBW: Antidepressants increase risk of suicidal thoughts in children &lt;12, adolescents, and young adults (18-24 y.o.) BBW: Not FDA approved for treatment of Bipolar Disorder Depression Approved for treatment of nocturnal enuresis in children ≥6 y.o.</td>
</tr>
</tbody>
</table>
### Overview of Tricyclic Antidepressants (TCAs)\(^{2,13,16,19,20}\)

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</table>
| **Elavil** | Amitriptyline | Yes        | Increases concentration of serotonin and/or norepinephrine in the CNS | Initial: 10-25 mg/day  
Range: 100-300 mg/day | Weight gain, blurred vision, fatigue, constipation, headache, somnolence, dizziness, cardiac dysrhythmia, decreased liver function, QT prolongation | BBW: Antidepressants increase risk of suicidal thoughts in children <12, adolescents, and young adults (18-24 y.o.)  
BBW: Not FDA approved in children for Bipolar Disorder Depression |
| **Anafranil** | Clomipramine | Yes | Clomipramine appears to affect serotonin uptake while its active metabolite, desmethylclomipramine, affects norepinephrine uptake | Initial: 25 mg/day  
Range: 100-250 mg/day, increase every 4-7 days by 25 mg/day | Dizziness, somnolence, headache, urinary retention, mania, tremor, orgasm incapacity, weight gain or loss, hepatotoxicity, QT prolongation | BBW: Antidepressants increase risk of suicidal thoughts in children <12, adolescents, and young adults (18-24 y.o.)  
BBW: Not FDA approved for treatment of Bipolar Disorder Depression  
Approved for treatment of OCD in children ≥10 years |

### TCAs: Clinical Summary\(^{2,13,16,19,20}\)

1. The antidepressant effects of TCAs are normally seen after four or more weeks of drug therapy. Since they are very lipophilic compounds and highly protein bound, they tend to have longer half-lives and an increased potential for toxicity in the elderly.
2. There are numerous problems associated with the use of TCAs so they must be used with caution, if at all in the elderly, because of their adverse effects.
3. Blocking α1-adrenergic receptors can cause orthostatic hypotension or dizziness. Blocking muscarinic receptors causes the anticholinergic effects, such as dry mouth, blurred vision, urinary retention, and constipation.
4. Blocking H1 histamine receptors results in sedation and weight gain.
5. TCAs are the most lethal antidepressants in overdose and not well-tolerated overall, thus, are seldom considered first-line for patients with depression. TCAs may also produce cardiac arrhythmias and heart block in susceptible individuals.
6. One important side effect of TCAs is their ability to cause cognitive impairment. This side effect is often overlooked because memory and concentration problems are expected to happen in the elderly to some degree.
7. Orthostatic hypotension is particularly dangerous in the patients who are volume-depleted, or on antihypertensive drugs. This can increase the risk of falls, potentially leading to increased risk of hip fracture.

8. Anticholinergic side effects such as dry mouth, blurry vision, constipation, urinary retention, and tachycardia are most problematic with amitriptyline.

9. TCAs are contraindicated in patients with benign prostatic hyperplasia (BPH) and narrow angle glaucoma, and should generally be avoided in elderly patients.

Test Yourself
TCAs block α1-adrenergic receptors which is responsible for producing which adverse effect?

A. Bradycardia
B. Diarrhea
C. Orthostatic hypotension
D. None of the above

The answer is C: Orthostatic hypotension.

Overview of Selective Serotonin Receptor Inhibitors (SSRIs) 2,13,16,19,20
Fluoxetine, Citalopram, Escitalopram, Paroxetine, Sertraline, Fluvoxamine, Vortioxetine, Vilazodone

- These drugs work mainly on SER reuptake inhibition. SSRIs have equivalent efficacy in depression, but side effects differ slightly.
- The SSRIs dosage vary, but initiate with low doses and titrate slowly to improve tolerability. Adverse reactions include somnolence, insomnia, nausea, diaphoresis, diarrhea, tremors, sexual dysfunction, and headache.

Did You Know?
Black Box Warning: Antidepressants increase risk of suicidal thoughts in children, teens, and young adults.
## Overview of Selective Serotonin Receptor Inhibitors (SSRIs) \(^2,13,16,19,20\)

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<td>SSRI</td>
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<tr>
<td>Paxil</td>
<td>Paroxetine</td>
<td>Yes</td>
<td>Inhibits serotonin reuptake from brain synapse stimulated serotonin activity in the brain</td>
<td>Initial: 20 mg/day (Range: 20-60 mg/day)</td>
<td>Weakness, tremor, somnolence, insomnia, diarrhea, constipation, diaphoresis, decreased libido</td>
<td>Paxil CR(^\circ) incorporates a degradable polymeric matrix (Genomatrix(^\text{TM})) to control dissolution rate over a period of 4-5 hours. An enteric coating delays the start of drug release until tablets have left the stomach. Not approved for children or bipolar. (\text{BBW:}) Increased risk of suicidal ideation.</td>
</tr>
<tr>
<td>Zoloft</td>
<td>Sertraline</td>
<td>Yes</td>
<td>Selective inhibitory effects of presynaptic 5-HT reuptake. Very weak effects on NE and DA uptake.</td>
<td>Initial: 25 mg/day (Range: 25-200 mg/day)</td>
<td>Somnolence, insomnia, nausea, diaphoresis, diarrhea, tremors, decreased libido, headache, fatigue</td>
<td>(\text{BBW:}) Antidepressants increase risk of suicidal thoughts. Buspirone (15-60 mg/day) may be useful in treatment of sexual dysfunction with a SSRIs. May exacerbate tics in Tourette's.</td>
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</tbody>
</table>
## Overview of Selective Serotonin Receptor Inhibitors (SSRIs)\(^2,13,16,19,20\)

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<tr>
<td><strong>Prozac</strong></td>
<td>Fluoxetine</td>
<td>Yes</td>
<td>Inhibits CNS neuron serotonin reuptake; minimal or no effect of reuptake of NE or DA</td>
<td>Depression/OCD/PMDD/bulimia 20 mg/day may increase by 20 mg after several weeks Max: 80 mg/day</td>
<td>Insomnia, headache, somnolence, anxiety, nervousness, decreased libido</td>
<td>ECG may reveal S-T segment depression. 15-60 mg/day buspirone and cyproheptadine may be useful in treatment of sexual dysfunction due to SSRI; weekly capsules equivalent to 90 mg fluoxetine. <strong>BBW:</strong> Antidepressants increase suicidal ideation</td>
</tr>
<tr>
<td><strong>Luvox</strong></td>
<td>Fluvoxamine</td>
<td>Yes</td>
<td>Inhibits CNS neuron serotonin uptake; minimal or no effect on reuptake of NE or DA</td>
<td>Initial: 50 mg/day Range: 50-300 mg/day</td>
<td>Headache, insomnia, somnolence, weakness, diarrhea, anorexia, abnormal ejaculation</td>
<td><strong>BBW:</strong> Antidepressants increase risk of suicidal thoughts in children, adolescents, and young adults (18-24 y.o.). Not FDA-approved for Bipolar Disorder. Fluvoxamine is FDA-approved for the treatment of OCD in children ≥8 y.o.</td>
</tr>
</tbody>
</table>
1. The SSRIs have replaced TCAs as first line therapy for depression.
2. There is wide inter-patient variability between the SSRIs with regard to their metabolism and pharmocokinetics.
3. SSRIs have favorable side effect profiles and low toxicity in cases of overdose.
4. The frequency and severity of anticholinergic, cardiovascular, and sedative side effects are lower with SSRIs, relative to TCAs. However, gastrointestinal problems (nausea, vomiting, and anorexia), male and female sexual dysfunction, and weight loss are more common.
5. In overdose, SSRIs can cause serotonin syndrome, which is characterized by myoclonus, diarrhea, confusion, psychomotor agitation, hyperreflexia, tremors, motor instability, fevers, nausea, vomiting, and changes in blood pressure.
6. Serotonin syndrome is more likely to occur in patients receiving interacting serotonergic drugs such as tramadol, linezolid, triptans, dextromethorphan, MAO inhibitors, lithium, and other antidepressants.
7. Optimal clinical response may not be seen for several weeks, but a subset of patients may report benefit after one week. A minimum of 6-12 weeks is recommended for an initial episode of mild to moderate depression.
8. Continued treatment for 4-9 months is generally indicated for patients who respond to acute treatment of a unipolar depressive episode.
9. Loss of erectile or ejaculatory function in men and loss of libido and lack of orgasm in both sexes is associated with SSRI use.
10. Citalopram is not recommended in patients with congenital long QT syndrome since dose-dependent QT prolongation has been reported in association with use.

**Serotonin/Norepinephrine Reuptake Inhibitors (SSNRIs)**

Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran, Levomilnacipran

- The serotonin / norepinephrine (SER/NE) reuptake inhibitors vary in their mechanisms and selectivity of action. For example, venlafaxine is an SSNRI with weak inhibition of dopamine reuptake and is selective for 5-HT (serotonin) at lower dosages and has increased NE affinity as dosages increase.
- Duloxetine works similarly to TCAs by inhibiting the reuptake of both NE and SER but does not affect histamine H1 or muscarinic receptors.
- Milnacipran is an inhibitor of NE and SER reuptake with no significant activity for serotonergic, alpha- and beta-adrenergic, muscarinic, histaminergic, or dopaminergic receptors.
- Levomilnacipran is the more active enantiomer (a pair of chemical compounds that are mirror images of each other) of milnacipran and also a potent inhibitor of NE and SER reuptake.
- Milnacipran is approved in the US for fibromyalgia treatment, whereas levomilnacipran is approved for depression.

*Please note!*

**SSNRIs are antidepressants of choice in patients with chronic pain syndromes.**
### Serotonin/Norepinephrine Reuptake Inhibitors (SSNRIs) ²,¹³,¹⁶,¹⁹,²⁰

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<tr>
<td>Pristiq</td>
<td>Desvenlafaxine</td>
<td>Yes</td>
<td>Potent and selective serotonin and norepinephrine reuptake inhibitor</td>
<td>50-400 mg/day Decrease dose in renal impairment HD-50 mg/day; gradually taper dose when D/C</td>
<td>Dizziness, insomnia, diarrhea, diaphoresis, palpitation, hypertension, orthostatic hypotension</td>
<td><strong>BBW:</strong> Antidepressants increase risk of suicidal thoughts in children, adolescents, and young adults (18-24 y.o.) Not FDA approved in children or for Bipolar Disorder</td>
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<tr>
<td>Cymbalta</td>
<td>Duloxetine</td>
<td>Yes</td>
<td>Potent inhibitor of neuronal serotonin and norepinephrine reuptake and a weak inhibitor of dopamine reuptake</td>
<td>Initial: 30 mg/day Range: 30-90 mg/day</td>
<td>Dizziness, insomnia, diarrhea, diaphoresis, palpitation, hypertension, orthostatic hypotension</td>
<td><strong>BBW:</strong> Antidepressants increase risk of suicidal thoughts in children, adolescents, and young adults (18-24 y.o.) Not FDA approved in children or for Bipolar Disorder</td>
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<td>Effexor</td>
<td>Venlafaxine</td>
<td>Yes</td>
<td>Potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake</td>
<td>Initial: 37.5-75 mg/day Range: 75-225 mg/day</td>
<td>Dose-related HTN, headache, somnolence, dizziness, anxiety, nausea, abnormal ejaculation/vaginism</td>
<td><strong>BBW:</strong> Antidepressants increase risk of suicidal thoughts in children, adolescents, and young adults (18-24 y.o.) Not FDA approved in children or for Bipolar Disorder</td>
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### SNRI-Like Antidepressants ²,¹³,¹⁶,¹⁹,²⁰

Miscellaneous SER/NE reuptake inhibitors vary in their mechanisms of action and pharmacology.


**Bupropion**

- Reuptake inhibitor of 5-HT and NE, but not DA, no anticholinergic side effects.
- Initial: 150 mg/day, Range: 150-300 mg/day.
- ADRs: Nausea, nervousness, insomnia, less weight gain and sexual dysfunction, seizures (higher doses).

**Nefazodone**

- Inhibits neuronal reuptake of SER and NE, alpha₁ receptors; no affinity for cholinergic, DA.
- Initial: 100 mg/day, Range: 200-600 mg/day.
- ADRs: Headache, drowsiness, insomnia, agitation, dizziness, dry mouth, nausea, constipation, sexual dysfunction.
Trazodone

- Inhibits reuptake of SER, causes adrenoreceptor subsensitivity and induces changes in SER presynaptic receptor receptors.
- Trazodone also blocks histamine and alpha-1 receptors.
- Dosing: Recommend sustained-release formulation for better tolerability and adherence. Start at 150 mg once daily at HS. May increase by 75 mg/day every three days to a maximum dose of 375 mg/day. Titrate dose downward, if clinically-indicated.
- ADRs: Sedation, dizziness, dry mouth, nausea, nervousness, insomnia, headache, sexual dysfunction, blurry vision, priapism (rare).

Miscellaneous SNRI-Like Antidepressants $^{2,13,16,19,20}$

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</tr>
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<tbody>
<tr>
<td>Wellbutrin</td>
<td>Buproprion</td>
<td>Yes</td>
<td>The primary mechanism of action is though to be dopaminergic and/or noradrenergic</td>
<td>Initial: 150 mg/day Range: 150-300 mg/day Extended release and sustained release, and immediate release are available</td>
<td>Dry mouth, weight change, hypertension, abnormal dreams, lowering of seizure threshold, dizziness, anxiety, agitation, hepatotoxicity</td>
<td>BBW: Antidepressants increase risk of suicidal thoughts in children, adolescents, and young adults (18-24 y.o.) Not FDA approved in children or for Bipolar Disorder or for use in children BBW: Serious neuropsychiatric events including depression, suicidal thoughts, and suicide, have been reported use Used for smoking cessation without FDA approval</td>
</tr>
<tr>
<td>Desyrel</td>
<td>Trazodone</td>
<td>Yes</td>
<td>Inhibits reuptake of serotonin, causes adrenoreceptor subsensitivity, and reduces significant changes in 5-HT presynaptic receptor adrenoreceptors Trazodone also significantly block histamine (H$_2$) and alpha$_2$-adrenergic receptors</td>
<td>Initial: 50 mg/day Range: 150-300 mg/day</td>
<td>Constipation, diarrhea, dizziness, headache, insomnia, somnolence, dream disorder, feeling nervous, priapism, prolonged QT interval, torsades de pointes</td>
<td>BBW: Antidepressants increase risk of suicidal thoughts in children, adolescents, and young adults (18-24 y.o.) Not FDA approved in children or for Bipolar Disorder or for use in children At least 14 days between MAD-1 and mirtazapine use</td>
</tr>
</tbody>
</table>

Atypical Antidepressants $^{2,13,16,19,20}$

Mirtazapine:

- Has central presynaptic alpha$_2$-adrenergic antagonist effects, resulting in increased release of NE and SER. It is also a potent antagonist of 5-HT$_2$ and 5-HT$_3$ serotonin receptors and H1 histamine receptors and a moderate peripheral alpha$_1$-adrenergic and muscarinic antagonist, no SSRI effect
- Initial: 15mg/day, Range 15-45 mg/day.
- ADRs: Somnolence, dyslipidemia, dry mouth, weight gain, and constipation.
Atypical Antidepressants \[2,13,16,19,20\]

<table>
<thead>
<tr>
<th>Brand Name</th>
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<th>Mechanism of Action</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remeron</td>
<td>Mirtazapine</td>
<td>Yes</td>
<td>Central presynaptic alpha-2 adrenergic antagonist effects, which results in increased release of norepinephrine and serotonin</td>
<td>Initial: 15 mg/day Range: 15-45 mg/day</td>
<td>Disturbance in thinking, dream disorder, increase in LFT, constipation, dry mouth, weight gain, hypertriglyceridemia, hypercholesterolemia</td>
<td>BBW: Antidepressants increase risk of suicidal thoughts in children, adolescents, and young adults (18-24 y.o.) Not FDA approved in children or for Bipolar Disorder or for use in children At least 14 days between MAO-I and mirtazapine use</td>
</tr>
</tbody>
</table>

Test Yourself

Which of the following antidepressants work by serotonin and norepinephrine reuptake inhibition?

A. Venlafaxine
B. Desvenlafaxine
C. Levomilnacipran
D. All of the above

The answer is D: All of the above.

Discontinuing Antidepressants \[2,13,16,19,20\]

- Abrupt discontinuation of antidepressants can lead to withdrawal symptoms, such as agitation, anxiety, insomnia, jitteriness, and potential re-emergence of depressive symptoms.
- There are no evidence-based guidelines for tapering therapy, but this should be done over at least several weeks with consideration to the half-life of the antidepressant.
- Antidepressants with shorter half-lives may need to be tapered more conservatively. In addition, the length of antidepressant therapy should also be considered, lengthening the taper in cases of patients on several years of therapy.

Antidepressant Black Box Warning

- The FDA has recommended that adults treated with any antidepressant medication, particularly for the indication of depression, be watched closely for worsening of depression and/or suicidal behavior or thinking.
- Monitoring should be particularly vigilant during initiation of therapy and during any change in dosage. Patients exhibiting any worsening of depressive symptoms or increased suicidal thinking/behavior should be promptly evaluated by their healthcare provider.

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• These recommendations are consistent with current labeling for each product.

Monamine Oxidase Inhibitors \(^{2,13,16,19,20}\)
MAOIs increase endogenous concentrations of epinephrine, NE, DA, and SER through inhibition of the enzyme (monoamine oxidase) responsible for the breakdown of these neurotransmitters. Numerous adverse reactions, contraindications, drug interactions, and dietary restrictions exist with MAOIs.

- Phenylzine
  - Initial: 15 mg/day, Range 30-90 mg/day
- Tranylcypromine
  - Initial: 10 mg/day, Range 20-60 mg/day
- Selegiline (Transdermal)
  - Initial: 9 mg/24 hours or 12 mg/24 hours

Depression Case Study

Chief Complaint
"I'm having difficulty concentrating at work and I don't have any energy."

History of Present Illness
RB is a 39 year-old married woman who presents to her family doctor for her annual exam and Pap smear. She also relates an unintentional ten pound weight loss over the last three months. She complains of feeling exhausted and has had trouble falling asleep. When questioned, RB admits to a decline in sexual activity with her husband and a general lack of interest in her usual activities, such as jogging, volunteer work, and shopping. She admits to periodic crying episodes, but denies any suicidal thoughts. RB relates that these changes in her mood began approximately two months ago and has been steadily worsening.

Medications
Ethinyl estradiol 30mcg plus norgestrel 0.3mg 28-day once daily, acetaminophen 500mg one every eight hours prn tension headaches.

Family History
Both parents are alive and well and her older sister is being treated for depression.

Social History
RB works part-time as an RN and has two healthy male children, ages 9 and 12. She denies any serious stress or psychosocial problems at home or at work.

Physical Exam
All within normal limits:
- Vital signs: 120/82mmHg
- Pulse 72
- Temp 36.0

Diagnosis
Major depressive episode
Case Study Questions
What target symptoms of depression does RB display?
Difficulty concentrating at work, lack of energy, unintentional weight loss, feeling exhausted, trouble falling asleep, decline in sexual activity, anhedonia, and periodic crying episodes.

Explore past medical history.
- Any suicidal ideation (if "yes", then ask if she has an active plan)?
- Any prior history of depression (or family history) and previous response to therapy?
- Ask about any drug allergies and allergy description.
- Any possibility of pregnancy?
- Ask about formulary coverage.
- Ask about use of OTCs and dietary supplements

What non-pharmacologic modalities could be recommended?
- Psychotherapy
- Counseling
- Prayer or pastoral care
- Exercise
- Rest
- Improved sleep hygiene
- Insight training

What drug therapy regimen might you recommend?
- Any SSRI would be appropriate initially: citalopram, fluoxetine, paroxetine, sertraline, other antidepressants (e.g. bupropion) or SNRI (e.g. venlafaxine) would also be appropriate.
- Start at lower end of initial dose and increase dosage if clinically-indicated and as tolerated within four weeks.
- If no clinical response after eight weeks of full therapeutic dose, consider a different antidepressant of a different class.
- Generally, total treatment duration of 9-12 months is optimal to avoid future depressive relapse.

How should drug therapy be monitored in RB?
- Monitor for drug efficacy by monitoring target symptoms, such as energy level, appetite, concentration, mood, etc.
- Monitor for SSRI (or other antidepressant) adverse effects, such as insomnia, CNS activation, jitteriness, tremor, nausea, diarrhea, headache, sexual dysfunction, and dry mouth.

How should RB be counseled about her drug therapy?
- Advise RB of the predictable side effects, but note that these should attenuate over time, with the possible exception of sexual dysfunction and dry mouth.
- Counsel RB to remain adherent while waiting for clinical response since these drugs may take about 3-4 weeks for initial therapeutic response and about eight weeks for significant response.
- RB should be counseled to contact her physician if her symptoms worsen, or do not improve in 3-4 weeks.

**Bipolar Disorder**

**Definition of Bipolar Disorder**

- Bipolar disorder is a cyclic mood disorder characterized by fluctuations in mood, energy, and behavior. Patients with bipolar disorder have chronic, recurrent episodes of major depression (unipolar depression), fluctuating with variable episodes of mania and/or hypomania (both defined later) during the course of the illness.
- Most patients with bipolar disorder require lifelong behavioral and pharmacological interventions.

**Did You Know?**

*Bipolar disorder was formerly called manic-depressive illness.*

**Definition of Bipolar Disorder**

- Bipolar I disorder is when patients experience one or more manic episodes and nearly always experience major depressive and hypomanic episodes.
- Bipolar II disorder is when patients experience recurrent major depressive episodes with hypomanic episodes. Patients have at least one hypomanic episode, at least one major depressive episode, in the absence of manic episodes.
- Patients with bipolar disorder may have cyclothymia, which is characterized by oscillating high and low moods, and if these episode occur with high frequency, it is called rapid cycling disorder.

**Epidemiology of Bipolar Disorder**

- The lifetime prevalence of bipolar disorder in US adults is estimated to be approximately 1%.
- However, some surveys that include all subtypes of bipolar (e.g. rapid cycling, cyclothymia, mild disease), the prevalence is closer to 4.5%.
- The disorder occurs about equally in men and women, with bipolar II being more common in women.
- The mean age of onset for bipolar disorder is 18 and 20 years.

**Etiology and Pathogenesis of Bipolar Disorder**

- More than half of patients with bipolar disorder have a biologic relative with some type of mood disorder.
• Family, twin, and adoptive studies have demonstrated that genetic factors are involved, though no single gene has been isolated.
• The exact cause of bipolar disorder is unknown, but disease development is likely complex and influenced by developmental, genetic, neurobiological, anatomical, and psychosocial factors.
• Altered synaptic and circuit functioning accounts for mood and cognitive changes, rather than dysfunction of individual neurotransmitters.

Test Yourself
What is the mean age of onset for bipolar disorder?

A. 10-12 years
B. 18-20 years
C. 56-58 years
D. >65 years

The answer is B: 18-20 years.

Diagnostic Criteria for a Manic Episode DSM-V
Criteria A through D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder:

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy lasting at least one week and present most of the day, nearly every day.
B. During the period of mood disturbance and increased energy, three or more of the following symptoms are present to a significant degree and represent a noticeable change from usual behavior:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep.
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (attention too easily drawn to unimportant or irrelevant external stimuli).
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.
Pneumonic for Symptoms of Mania: DIG FAST

Symptoms of mania can be remembered using the following pneumonic:

- Distractibility
- Indiscretion and irresponsibility (buying sprees, hypersexuality)
- Grandiosity
- Flight of ideas
- Activity levels increase
- Sleep decrease
- Talkativeness and tangential thoughts (digressive or irrelevant thoughts/speech)

Hypomania

- A hypomanic episode is similar to a manic episode, but in hypomania the elevated mood and/or energy level lasts at least four consecutive days (versus one week or more in mania) and is present most of the day, nearly every day.
- The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization.
- If there are psychotic features, the episode is, by definition, manic.
- Individuals who report having hypomanic episodes are generally productive and do not experience the same degree of psychosocial dysfunction as patients with mania.

Secondary Causes of Mania

Certain medical conditions can induce manic episodes, or mania-like symptoms, such as:

- CNS disorder (e.g., head injuries, brain tumors)
- Electrolyte disturbances (e.g., glucose, sodium)
- Endocrine disorders, including Addison’s Disease, Cushing’s Disease and thyroid disorder
- Infections, including HIV, encephalitis, and neurosyphilis

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• Sleep deprivation

Secondary Causes of Mania

Certain medications or drugs of abuse can induce mania, such as:

• Alcohol intoxication
• Drug withdrawal states
• Antidepressants, especially SSRIs upon initiation
• CNS stimulants: amphetamines, cocaine, sympathomimetics, dopamine agonists
• Hallucinogens (e.g., LSD, PCP)
• Systemic steroids (e.g., testosterone, ACTH, high-dose corticosteroids)
• Thyroid preparations

Substance Abuse Co-Morbidity

• Among individuals with bipolar disorder, the lifetime prevalence of substance use disorders was 60% in one US study.
• The lifetime prevalence of anxiety disorders was 75% in the same study.
• Concurrent abuse of alcohol, benzodiazepines, and other substances has often been reported in those with bipolar disorder.
• Alcohol dependence has been reported in 46% of bipolar patients.

General Approach to Treating Bipolar Disorder

• Management of bipolar disorder must be individualized to the patient.
• Treatment will vary greatly depending on if a patient is acutely manic or hypomanic, the clinical features and severity of mania, rapidity of cycling, risk of suicide, age of patient, pregnancy status, drug interactions, history of previous response.
• Acute treatment of manic episodes in bipolar patients differs markedly from maintenance treatment.
• Concurrent substance abuse disorders should be addressed medically and may require tapering and psychosocial intervention.

Examples of Supportive Therapy for Bipolar Disorder

Supportive therapy may include one or more of the following therapies:

✓ Proper nutrition, proper sleep hygiene, exercise, and stress reduction
✓ Mood charting
✓ Counseling and insight-oriented psychotherapy
✓ Couples or family therapy
✓ Cognitive behavioral therapy
Pharmacotherapy for Bipolar Disorder\textsuperscript{19-21,24}

1. Lithium and valproic acid were historically used for treating acute mania and prophylaxis of recurrent mania and depressive episodes. However, newer alternatives exist.
2. Anticonvulsants (e.g., lamotrigine, carbamazepine, and valproate) may in some cases be better-tolerated than lithium, given lithium's low therapeutic index.
3. Atypical antipsychotics (e.g., aripiprazole, olanzapine, risperidone, quetiapine, and ziprasidone) may be used as alternatives, or as adjunctive treatment, especially when psychotic features are present.
4. Although oxcarbazepine has been studied for both acute and maintenance therapy, evidence does not support its routine use for either indication.

Test Yourself
When treating acute mania, older antipsychotic drugs such as thioridazine are preferred over new atypical antipsychotics, such as olanzapine.

A. True
B. False

The answer is B: False.

Lithium\textsuperscript{21,24}

- Lithium is indicated for both acute mania treatment and maintenance therapy.
- Lithium works by altering cation transport across cell membranes in nerve and muscle cells. It influences reuptake of SER and NE, and postsynaptic Dopamine-2 (D2) receptor hypersensitivity is inhibited.
- The typical dosing range is 900-2400 mg/day in 2-4 divided doses with meals (depends on the formulation). Sustained-release preparations are better tolerated.
- Adverse reactions include bradycardia, EKG abnormalities, thinning hair, diabetes insipidus, tremor, ataxia, confusion, dystonia, vertigo, polyuria, thyroid dysfunction, polydipsia, and dry mouth. Patients on lithium should be monitored for nephrogenic diabetes insipidus (polyuria, polydipsia, dilute urine).
- The approximate therapeutic serum level for maintenance therapy is 0.6-1.2 mEq/L.
- Lithium is contraindicated in pregnancy, having been associated with Epstein's anomaly, a type of neonatal tricuspid valve abnormality. It is generally recommended that breast-feeding be avoided during maternal use of lithium. However, treatment may be continued in certain patients.
- Thiazide diuretics can decrease lithium excretion, predisposing patients to lithium toxicity. Follow clinical response and monitor for toxicity for treatment of acute manic episodes. Neurotoxicity, sometimes permanent, has been reported in lithium overdose.
Valproic Acid\textsuperscript{21,24}

- Valproic acid works by increasing availability of gamma amino butyric acid (GABA) to CNS neurons, or by enhancing GABA activity or its action at postsynaptic receptor sites. Valproate reduces or prevents recurrent manic, depressive and mixed episodes and is sometimes used in rapid cycling disorder with or without concurrent lithium.

- The dosing range is 750-3000 mg/day once daily for extended or sustained-release, or in divided doses, depending on the formulation. Dosage is titrated to clinical response and to a serum level of 50-125 mcg/mL. Divalproex sodium extended-release tablets may be better tolerated than plain release valproate.

- Adverse effects include headache, GI disturbances, alopecia, tremor, somnolence, dizziness, weight gain, thrombocytopenia, and hepatotoxicity.

- Liver function tests and platelets should thus be monitored at 6-12 month intervals.

- Valproic acid is contraindicated in pregnancy, as its use has been associated with neural tube defects, such as spina bifida. A pregnancy registry is available to women exposed to valproic acid while pregnant. Patients may enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling (888) 233-2334, or by visiting: \url{www.aedpregnancyregistry.org}

- Early signs and symptoms of hepatotoxicity may include decreased appetite, gastrointestinal distress (nausea, vomiting, abdominal pain), edema, malaise, and easy bruising.

\textbf{Did You Know?}

\textit{Liver enzyme inducing drugs, such as rifampin, carbamazepine, and phenobarbital may decrease the serum levels and effectiveness of valproate.}
**Lithium and Valproic Acid**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Gen. Avail.</th>
<th>Mechanism of Action</th>
<th>Dosing</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Eskalith (Capsule 300 mg)</td>
<td>Lithium Carbonate</td>
<td>Yes</td>
<td>Alters caution transport across cell membrane in nerve and muscle cells; influences reuptake of serotonin and/or norepinephrine; postsynaptic D2 receptor supersensitivity is inhibited</td>
<td>900-2400 mg/day in 2-4 divided doses with meals</td>
<td>Bradycardia, arrhythmias, EKG abnormalities, dry or thinning hair, folliculitis, tremor, ataxia, coma, confusion, dystonia, fatigue, vertigo</td>
<td>Maintenance therapy: Serum Lithium 0.6-1.2 mEq/L. Acute mood episode: Serum Lithium 1.0-1.2 mEq/L taken 8-12 hours after last dose. <strong>BBW:</strong> Lithium toxicity is closely related to serum concentrations and can occur at therapeutic doses.</td>
</tr>
<tr>
<td>Eskalith CR (450 mg ER tablet)</td>
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<tr>
<td>Lithobid (300 mg ER tablet)</td>
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**Anticonvulsants (used in Bipolar Disorder)**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Depakote (ER)</td>
<td>Divalproex Sodium</td>
<td>Yes</td>
<td>Increases availability of gamma-aminobutyric acid (GABA) to brain neurons or may enhance the action of GABA or mimic its action at postsynaptic receptor sites</td>
<td>750-3000 mg po/day once daily on in divided doses for delayed release divalproex</td>
<td>Headache, nausea, vomiting, diarrhea, alopecia, tremor, somnolence, dizziness</td>
<td>Serum concentration of VPA: 50-125 mcg/mL or clinical response. <strong>BBW:</strong> Hepatic failure/pancreatitis/teratogenic effects.</td>
</tr>
</tbody>
</table>

**Carbamazepine**

- The exact mechanism of action of carbamazepine for bipolar is unknown. The drug depresses activity in the nucleus ventralis of the thalamus, decreases synaptic transmission, and limits influx of sodium ions across cell membrane.
- The dosing range is 400-1800 mg/day in 2-4 divided doses with food. The drug is titrated slowly to desired effect.
- Adverse reactions include confusion, dizziness, nystagmus, somnolence, blurred vision, diplopia, Stevens Johnson Syndrome (rare), GI side effects, weight gain, and blood dyscrasias.

**Carbamazepine**

- Carbamazepine is not first-line for bipolar disorder and is usually reserved for those who do not respond to lithium, or for rapid cycling disorder.
- Carbamazepine causes significant CYP450 enzyme induction, numerous isoforms affected, including CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, and CYP3A4, thus a multitude of drug interactions.
• The drug is also metabolized mainly by CYP3A4. Thus, drugs that inhibit this isoform will prolong carbamazepine half-life and drugs that induce CYP3A4 will shorten the drug’s half-life. Thus, carbamazepine induces its own metabolism.

**Did You Know?**

Carbamazepine is potentially teratogenic and has also been associated with neural tube defects.

---

**Test Yourself**

Drugs used in the treatment of bipolar disorder that are contraindicated in pregnancy include:

A. Carbamazepine  
B. Lithium  
C. Valproic acid  
D. All of the above

The answer is D: All of the above.

---

**Lamotrigine** 19-21,24

• Lamotrigine inhibits the release of glutamate and inhibits voltage-sensitive sodium channels.

• The initial dose is 25 mg/day on weeks 1-2, then increased to 50 mg/day on weeks 3-4, then increased to 100 mg/day for week five, then increased to 200 mg/day after week six if necessary and as tolerated.

• Adverse effects are GI complaints, impaired memory, ataxia, dizziness, sedation, and rash.

**Did You Know?**

Black Box Warning: “Severe and potentially life-threatening skin rashes requiring hospitalization have been reported; risk may be increased by co-administration with valproic acid.”
### Carbamazepine and Lamotrigine

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lamical</td>
<td>Yes</td>
<td>Inhibits release of glutamate and voltage-sensitive sodium channels</td>
<td>Initial: 25 mg/day for weeks 1 and 2, then increase to 50 mg/day for weeks 3 and 4, then increase to 100 mg/day week 5. <strong>Maintenance</strong>: Increase dose to 200 mg/day beginning week 6. When combined with valproate, initial and titration dosing should be decreased by 50% to minimize the risk of a serious rash.</td>
<td>Nausea, chest pain, edema, rash (non-serious), vomiting, somnolence, fatigue</td>
<td><strong>BBW</strong>: Severe and potentially life-threatening skin rashes requiring hospitalization have been reported; risk may be increased by co-administration with valproic acid, higher than recommended starting doses, and rapid dose titration.</td>
</tr>
<tr>
<td>Tegretol</td>
<td>Carbamazepine</td>
<td>Yes</td>
<td>In addition to anticonvulsant effects, carbamazepine has anticholinergic, antineuralgitic, antidiuretic, muscle relaxant, antimanic, antidepressive, and antiarrhythmic properties</td>
<td>200-1800 mg/day in 2-4 divided doses with food (doses should slowly be increased according to clinical response and adverse events)</td>
<td>Common: hyper- / hypotension, lightheadedness, NV, clumsiness, confusion, dizziness, nystagmus, somnolence, blurred vision, diplopia. Serious: AV block, Stevens-Johnson syndrome, nephrotoxicity, hyponatremia, angioedema.</td>
<td>Carbaltol capsules can be opened and contents sprinkled over food. Autol induces its own metabolism. Instruct pt. to report use of an MAO-I w/in 14 days prior to initiation of drug therapy. May decrease effectiveness of oral contraceptives with concurrent use; recommend additional form. of birth control.</td>
</tr>
</tbody>
</table>

### Atypical Antipsychotics

- All drugs in this class have some degree of dopamine blockade on various dopamine receptor subtypes.
- A black box warning exists for all drugs in this class of increased risk of mortality in patients with dementia.
- A recent label warning includes cautions that neonates can develop extrapyramidal symptoms (EPS) and withdrawal symptoms with third trimester exposure.
- May cause weight gain, sometimes significant and potential glucose intolerance, except ziprasidone.
- Atypical antipsychotics are a non-homogeneous class of drugs. Please see the tables that follow for specific doses, side effects, etc.
<table>
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</tr>
</tbody>
</table>
| Zyprexa | Olanzapine | Yes | **Potent Antagonism:** 5-HT₂A, 5-HT₂C, D₁-₂, H₁, Alpha-1  
**Moderate Antagonism:** 5-HT₃  
**Mucarinic M1-5 Weak Antagonism:** GABA-A, BZD, Beta-AR | **PO:** Schizophrenia: 5-10 mg/day initial, adjust by 5 mg/day q 1 week up to max recommended dose of 20 mg/day (30-50 mg/day have been used)  
Bipolar Mania (Acute): 10-15 mg/day, increase by 5 mg q 24 hrs. to max dose of 20 mg/day, dosage range of 5-20 mg/day if used in combo with Li or VPA  
IM: Agitation (Acute): 10 mg q 2-4 hrs. to assess for response (max 30 mg/day) | Sedation, orthostasis, weight gain, somnolence, dose dependent EPS | BBW: Increased risk of mortality in patients with dementia |
| Seroquel | Quetiapine | Yes | Antagonism of receptors in brain: D₁, D₂-5-HT₁₅/₆, 5-HT₃, H₁, Alpha-1, Alpha-2; active metabolite (norquetiapine) has high affinity for mucarinic M1 | **Immediate release:** Bipolar Depression/ Mania: 50 mg/day initial, day 2 increase to 100 mg/day, and then increase by 100 mg to target dose of 300 mg/day (800 mg/day in mania); max dose of 900 mg/day in depression and 800 mg/day in mania  
**Extended release:** Depression: 50 mg/day initial dose, day 2 increase to 100 mg/day, then increase by 100 mg/day to dose of 300 mg/day; Mania: 300 mg/day initial, day 2 increase to 600 mg/day, then adjust dose to 400-800 mg/day on day 3, depending on response/tolerability | Sedation, dizziness, headache, hyperlipidemia, somnolence | BBW: Increased risk of mortality in patients with dementia, increased risk of suicidal ideation in adolescents on antidepressants  
Low EPS and prolactin elevation risk; increased risk for cataracts, perform a lens test at baseline and every 6 months |
<table>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Geodon</td>
<td>Ziprasidone</td>
<td>Yes</td>
<td>High affinity for D₂, D₆, 5-HT₁₆, 5-HT₁₂, 5-HT₁₃, 5-HT₁₄, and Alpha₁-adrenergic; moderate affinity for histamine H₁ receptors; no appreciable affinity for Alpha2-adrenergic receptors beta-adrenergic receptors, 5-HT₃a, 5-HT₄, cholinergic, mu, sigma, or benzodiazepine receptors. Ziprasidone functions as an agonist at the D₂, 5-HT₁₆, and 5-HT₁₃ receptors and as an agonist at the 5-HT₁₄ receptor.</td>
<td>PO: Bipolar Mania (Acute): 40 mg bid Initial; may increase to 60 or 80 mg bid on day 2, avg. dose 40-80 mg bid; Bipolar Maintenance (adjunct to Li or VPA): Stabilized patient dose (range 40-80 mg bid); Schizophrenia: Initial 20 mg bid; increases if indicated at least q 2 days; maintenance range 20-100 mg bid (dosages &gt;80 mg bid not recommended); II: They: Agitation (Acute): 10 mg q 2 hrs. or 20 mg q 4 hr (max 40 mg/day); switch to PO ASAP.</td>
<td>Sedation, weight gain, QT prolongation</td>
<td>BBW: Increased risk of mortality in patients with dementia. Use caution with other medications that prolong QT interval.</td>
</tr>
<tr>
<td>Abilify</td>
<td>Aripiprazole</td>
<td>No</td>
<td>High affinity for D₂, D₆, 5-HT₁₆, 5-HT₁₂, 5-HT₁₄ receptors, moderate affinity for D₄, 5-HT₁₆, 5-HT₁₂, Alpha₁-adrenergic, and H₁ receptors; it also possesses moderate affinity for the serotonin reuptake transporter; no affinity for muscarinic (cholinergic) receptors; Aripiprazole functions as a partial agonist at the D₆ and 5-HT₁₂-receptors, and as an agonist at the 5-HT₁₆ receptor.</td>
<td>Schizophrenia: Sublingual: Initial 5 mg bid then increase to 10 mg bid after 1 week based on tolerability; daily doses &gt;20 mg/day in clinical trials did not appear to offer any additional benefits and increased risk of adverse effects; Bipolar Disorder: Sublingual: Initial Monotherapy: 10 mg bid, decrease to 5 mg bid if dose not tolerated; Combination Therapy (with lithium or valproate): 5 mg bid, may increase to 10 mg bid based on tolerability.</td>
<td>EPS, blood dyscrasias, orthostatic hypotension, QT prolongation, sedation, suicidal ideation</td>
<td>BBW: Increased risk of mortality in patients with dementia. Dissolve tablet under the tongue; avoid eating/drinking for 5-10 minutes.</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Generic Name</td>
<td>Gen. Avail.</td>
<td>Mechanism of Action</td>
<td>Dosing</td>
<td>Side Effects</td>
<td>Comments</td>
</tr>
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<tr>
<td>Saphris</td>
<td>Asenapine</td>
<td>No</td>
<td>High affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{5}, D_{2}, H_{1}, and Alpha1 and Alpha2-adrenergic receptors; moderate affinity for H_{2} receptors. Asenapine has no significant affinity for muscarinic receptors. The binding affinity to the D_{2} receptor is 19 times lower than the 5-HT_{2A} affinity.</td>
<td>Schizophrenia: Initial sublingual: 5 mg bid then increase to 10 mg bid after 1 week based on tolerability; daily doses &gt;10 mg/day in clinical trials did not appear to offer any additional benefits and increased risk of adverse effects. Bipolar Disorder: Initial sublingual: Initial Monotherapy: 10 mg bid, decrease to 5 mg bid if dose not tolerated. Combination Therapy (with lithium and valproate): 5 mg bid, may increase to 10 mg bid based on tolerability.</td>
<td>EPS, blood dyscrasias, orthostatic hypotension, QT prolongation, sedation, suicidal ideation.</td>
<td>BBW: Increased risk of mortality in patients with dementia. Dissolve tablet under the tongue; avoid eating/drinking for 5-10 minutes.</td>
</tr>
<tr>
<td>Invenga</td>
<td>Paliperidone</td>
<td>No</td>
<td>High affinity to α1, D_{2}, H_{1}, and 5-HT_{2C} receptors, and a low affinity for muscarinic and 5-HT_{2A} receptors, in contrast to risperidone. Paliperidone displays nearly 10-fold lower affinity for α2 and 5-HT_{2A} receptors, and nearly 3 to 5-fold less 5-HT_{1D} and 5-HT_{5} respectively.</td>
<td>PO: 6 mg once daily in the am, titration not required; increases of 3 mg/day are recommended if needed q 4 days in schizoaffective disorder or q 5 days in schizophrenia, up to max of 12 mg/day. IM: Test tolerability with oral paliperidone or risperidone; initial 234 mg on day 1, 156 mg 1 week later, maintenance 117 mg q month (range 39-234 mg).</td>
<td>Headache, tachycardia, somnolence, anxiety.</td>
<td>BBW: Increased risk for mortality in elderly patients with dementia. Shell from tablet may be seen in stool.</td>
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</table>
Atypical Antipsychotics 19-21,24,25

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Gen. Avail.</th>
<th>Mechanism of Action</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Comments</th>
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</table>
| Loxapine Inhalation 19,20,26

- The antipsychotic drug loxapine (Adasuve®) was recently approved by the FDA as a dry-powder inhalation for treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

- A single 10 mg inhaled dose is to be administered by a healthcare professional within a 24-hour period. This formulation is for acute use only using the single-use inhaler.

- After administration, patients must be monitored for signs and symptoms of bronchospasm at least every 15 minutes for at least one hour.

- As with older antipsychotic drugs, loxapine can be associated with extrapyramidal side effects, such as acute dystonic reactions, as well as neuroleptic malignant syndrome and orthostatic hypotension.

Panic Disorder

Definition of Panic Disorder 27-29

Panic disorder is a common anxiety disorder characterized by recurrent panic attacks, persistent worry and concern about having another attack, or worry about the implications and consequences of an attack.

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Panic attacks are discrete episodes of intense anxiety, fear or discomfort. The attacks may vary in frequency and intensity, have an abrupt onset, and often involve intense and irrational anxiety, a feeling of imminent danger or an urge to escape.

Most patients with panic disorder can be treated on an outpatient basis using a combination of psychological, or cognitive-behavioral therapy (CBT) and pharmacotherapy.

**Epidemiology of Panic Disorder** 27-29

- The 12 month prevalence of panic disorder in the US population of those age 15-54 years is 2.7%. The lifetime prevalence in this population is 4.7%.
- Women are twice as likely to be affected as men.
- First-degree relatives of patients with panic disorder are up to eight times more likely to develop panic disorder.
- Panic disorder follows a bimodal distribution in prevalence by age, with one peak in late adolescence (age 15-19) and a second peak at later life (age 35-50).
- Frequent visits to the emergency or urgent care and subspecialists often precede the diagnosis.

**Diagnostic Criteria for Panic Attacks DSM-V** 7

An abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and during which time four or more of the following 13 symptoms occur:

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feelings of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, light-headed, or faint
9. Chills or heat sensations
10. Paresthesias (numbness or tingling sensations)
11. Derealization (feelings of unreality) or depersonalization (being detached from oneself)
12. Fear of losing control or "going crazy"
13. Fear of dying

The abrupt surge of panic symptoms can occur from a calm state or an anxious state. In the DSM-V, panic attacks, panic disorders, and agoraphobia are diagnosed separately with individual criteria for each.
Diagnostic criteria for Panic Disorder include:

A. Recurrent, unexpected panic attacks (as described previously).
B. At least one of the attacks has been followed by a month or more of one or both of the following:
   1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, "going crazy").
   2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).
C. The disturbance is not attributable to the physiological effects of a substance (e.g., medication or illicit drug) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).
D. The disturbance is not better explained by another mental disorder. As examples, the panic attacks do not occur only in response to:
   - Feared social situations, as in social anxiety disorder.
   - Circumscribed phobic objects or situations, as in specific phobia.
   - Obsessions, as in obsessive-compulsive disorder.
   - Reminders of traumatic events, as in posttraumatic stress disorder.
   - Separation from attachment figures, as in separation anxiety.

Test Yourself
Men are twice more likely to develop panic disorder than women.

A. True
B. False

The answer is B: False.

Triggers of Panic-Like Episodes
By definition, patients with panic disorder experience panic attacks that occur unprovoked. However, in certain situations, a person is fully aware of the source of their fear and anxiety, whereas in panic disorder, these same symptoms are unprovoked, unexplained, and often occur out of the blue.
The following situations may trigger symptoms that mimic a panic attack:

- Being in confined spaces, such as elevators, passageways, and tunnels.
- Being in crowded places, such as shopping malls, public transport systems, and entertainment venues.
- Being in open spaces, such as traveling over bridges, high buildings, and over bodies of water.
- Meeting and socializing with new or unfamiliar people.
- Encountering an object which causes distress, such as arachnophobia (fear of spiders).
**Medications Associated with Panic Disorder** 27,28
Centrally-acting stimulants can produce panic-like symptoms, such as:

- Amphetamines
- LSD
- Caffeine (large amounts)
- Pseudoephedrine
- Ginseng (large amounts)

CNS depressant withdrawal can also produce panic-like symptoms, such as:

- Benzodiazepine withdrawal, especially if abrupt
- Alcohol withdrawal

**Etiology of Panic Disorder** 28,30
The exact cause of panic disorder is unknown and cannot be explained by a single sociological, developmental, or biological theory.

Several theories postulated to explain its pathogenesis and pathophysiology of panic disorder, such as:

- Noradrenergic model
- GABA-receptor model
- Serotonin model
- Dysregulation hypothesis
- The anticipatory anxiety, worry, and fear associated with individual panic attacks probably contributes to the development of panic disorder

**Pathophysiology of Panic Disorder** 28,30
A serotonin dysfunction, or dysregulation probably exists in patients with panic disorder; however, the precise nature of serotonin dysfunction in the disorder is unclear.

Clinical trials lend support to the serotonin theory since medications that increase brain serotonin levels significantly improve symptoms.

Serotonin deficiency alone may not fully explain the pathogenesis of panic disorder. Dysregulation of other neurotransmitters, such as gamma-aminobutyric acid (GABA), dopamine, norepinephrine, and cholecystokinin may also be involved in the pathogenesis of disease.

**Pathophysiology of Panic Disorder** 28,30
Dysregulation in central GABA activity has been implicated in the development of generalized anxiety.
The anticipatory anxiety, worry, and fear associated with individual panic attacks probably contributes to the development of panic disorder.

Changes in neuronal circuits (“fear pathways”) of patients with panic disorder and include the following:
- Reduced volumes in the amygdala and temporal lobe.
- Lowered amounts of creatine and phosphocreatine metabolites in the medial temporal lobe.
- Decreased cerebral glucose metabolism in amygdala, hippocampus, thalamus, and brain-stem.

**Nonpharmacological Therapy for Panic Disorder**

**Introduction**

The management of panic disorder involves a combination of psychological and often, pharmacological approaches. Cognitive-behavioral therapy (CBT) is a common intervention for panic disorder.

1. The techniques involved in CBT are diverse and involve insight training, continuous panic attack monitoring, anxiety management skills (e.g., deep breathing exercises and relaxation techniques), cognitive restructuring, and progressive exposure to panic attack triggers.
2. Graded exposure can reduce anticipatory anxiety and phobic avoidance.
3. Response rates to CBT may be improved by combining these methods with pharmacotherapy.
4. CBT requires that patients spend considerable time and discipline to learn and practice these exercises, even on a daily basis.
5. Patients must be willing to confront the panic-producing activities and monitor panic attacks regularly.
6. Family or group therapy, community-based support groups, and self-help techniques can be used.
7. Patients should avoid substances and chemicals that promote panic, such as caffeine, alcohol, and nicotine.
8. Adequate sleep, rest, relaxation, and stress-reducing techniques are important as supportive therapy.
9. The following are examples of a type of CBT, whereby the patient will self-affirm the following true statements:
   - "This panic episode may be uncomfortable for now, but it is not dangerous. No one has ever died from a panic attack."
   - "Panic attacks never last very long. The discomfort I’m feeling right now will pass in a few moments; then I will be fine again."

**Overview of Pharmacotherapy for Panic Disorder**

The SSRIs are effective for panic disorder and are now considered first line treatment.

Evidence has been found that fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, and the SNRI, venlafaxine are effective in treating panic disorder.

When a rapid control of panic symptoms is necessary, the benzodiazepines offer the advantage of faster symptom resolution.

A disadvantage of benzodiazepine use with long-term therapy is the possibility of physiological dependence. Monoamine oxidase inhibitors (MAOIs) may be effective, but reserved for refractory patients only.
SSRIs for Panic Disorder

There are different theories behind why the SSRIs work for panic disorders. Serotonergic neurons originate in fairly restricted areas of the brain stem and raphe region, but then project widely throughout the central nervous system. Projections to the frontal cortex may mediate mood, the hypothalamus projections appetite and sleep and the amygdala projections anxiety and fear response. Thus, SSRIs would be expected to have beneficial effects in patients with panic disorder.

While SSRIs are better tolerated than TCAs, they can produce adverse effects such as headaches, nausea, irritability, insomnia, sexual dysfunction, drowsiness, and tremors. SSRIs may also cause an acute increase in anxiety upon initiation. These adverse effects may be attenuated by initiating therapy with lower doses than are usually used for depression. For example, the current recommended starting doses for panic are fluoxetine 10 mg/day, paroxetine 10 mg/day, and sertraline 25 mg/day. The dose is increased as tolerated and therapeutic effects will generally not be evident until four weeks, with full response seen in about 8-12 weeks.

Did You Know?
The optimal duration of SSRI treatment for panic disorder has not been determined. The total duration of therapy appears to be 8-12 months.

Test Yourself
The class of drugs now considered first-line for treating panic disorder are the:

A. TCAs  
B. MAOIs  
C. SSRIs  
D. Lithium

The answer is C: SSRIs.

SSRIs for Panic Disorder: Drug Therapy Management Clinical Pearls

- Fluoxetine has a longer half-life and an active metabolite. It may be too “activating” for some patients and may actually worsen panic symptoms.
- Paroxetine has a shorter half-life, but can be dosed once daily with controlled-release form. It has some anticholinergic effects and may be more sedating for some patients.
- Sertraline may cause more diarrhea, but has fewer drug interactions than the SSRIs above and has an intermediate half-life enabling once daily dosing.
- Citalopram and escitalopram have intermediate half-lives, enabling once daily dosing. They have limited propensity to cause drug interactions.
**Benzodiazepines for Panic Disorder** 27,28,31,32
Benzodiazepines are very helpful for acute panic attacks due to their rapid anxiolytic effect. Thus, they are often used during the initiation phase of drug therapy. Later, they can be used to abort recurrent panic attacks.

These drugs may be helpful for bridging an SSRI since the SSRIs may have a 4-6 week lag-time. Clonazepam, lorazepam, diazepam, and alprazolam have been most widely studied in treating panic disorder, with clonazepam and alprazolam being the only two agents FDA-approved for this indication.

Common side effects include sedation, fatigue, ataxia, slurred speech, memory loss (amnesia), motor weakness, respiratory depression, tolerance, abuse potential, dependence, and withdrawal.

**Benzodiazepines: Clinical Pearls** 27,28,31,32
Benzodiazepines reduce attack frequency, anticipatory anxiety and phobic avoidance. Meta-analyses with these drugs show similar efficacy to SSRIs or TCAs.

Alprazolam has the fastest onset of action, due to greater lipid solubility and brain penetration, but has a short half-life. This may actually reinforce the need to take the drug more often and foster dependence, thus making it more prone to abuse.

Alprazolam extended release is available for BID use and may be less associated with abuse. Clonazepam has a longer half-life and has less intensive withdrawal symptoms on discontinuation.

**Test Yourself**
A history of substance abuse is a contraindication to benzodiazepine therapy.

A. True
B. False

The answer is A: True.

**Panic Disorder Case Study**

**Chief Complaint**
"I think I'm losing my mind."

**History of Present Illness**
BB is a 22 year-old healthy female who is a nursing assistant and attends evening classes at a local university. Three months ago while sitting in class, BB was struck by sudden feeling of terror and anxiety and felt that she was going to lose control. She reports the attack was accompanied by heart pounding, dizziness, and sweaty palms. The episode lasted 15 minutes, during which time she wanted to escape the confines of her classroom. She later dismissed the episode as being attributed to heavy caffeine use in the preceding days and lack of sleep.

Over the next eight weeks, BB experienced three more attacks; two at work and another while studying at home. These episodes were equally frightening and not associated with any immediate danger, yet BB felt terrified and thought she was going crazy. For the past five weeks BB has developed disabling anxiety and worries everyday about having more attacks and started skipping school. She now has visited her family doctor.
Physical Exam
Her physician found no remarkable findings on physical exam.

Past Medical History
BB has no medical problems and is not taking any medications, except occasional acetaminophen for dysmenorrhea. BB rarely drinks alcoholic beverages and does not use any recreational drugs.

Physical Exam
BB’s vital signs, laboratory findings, including blood chemistry, TSH, and ECG were normal.

Diagnosis
The physician believes that these episodes are panic attacks and gives BB a diagnosis of panic disorder.

Case Study Questions
1. What symptoms support the diagnosis of panic disorder?
   - BB stated, "I think I'm going crazy."
   - She had the sudden feeling of terror and anxiety and felt that she was going to "lose control".
   - She experienced heart palpitations, dizziness, and sweating.
   - She wanted to escape the confines of her front row seat, but there was no immediate danger or threat to her.
   - For the past five weeks, BB has developed disabling anxiety and worries every day about having more attacks and started skipping classes at school.

2. What other questions would you ask of BB if consulted?
   - Past history of previous response to therapy or family members' response to a medication.
   - Obtain a completed medication history, including OTC's and supplements, use of substances of abuse, especially CNS stimulants (e.g., cocaine, caffeine, and amphetamines).
   - Screen for any history of substance abuse and ask about any possible withdrawal from CNS depressants (e.g., barbiturates, alcohol, benzodiazepines).
   - Ask about any other potential psychiatric or medical co-morbidities, such as depression or insomnia.

3. What nonpharmacological therapy would be appropriate for BB?
   - Cognitive-behavioral therapy (CBT) that includes insight training, continuous panic attack monitoring, anxiety management skills (deep breathing exercises and relaxation techniques), cognitive restructuring, and progressive exposure to panic triggers.
   - Graded exposure to reduce anticipatory anxiety and phobic avoidance (if present in BB).
   - Group and family therapy, as well as patient support groups and patient education.

4. What pharmacologic strategy would be appropriate for treating BB?
   - Since BB's panic attacks are severe and she is avoiding school, a long-acting benzodiazepine, such as clonazepam would be appropriate to start. The initial dose of 0.25-0.5 mg is given at bedtime. The drug can be slowly increased and given once or twice daily as indicated and tolerated to a maximum of 4 mg daily.
• Simultaneously start an SSRI at a low dose, such as paroxetine 10 mg, sertraline 25 mg, citalopram 10 mg, or escitalopram 5 mg, all once daily in the morning.
  o The SSRI dose should be titrated up over 2-6 weeks and the benzodiazepine discontinued within 2-4 weeks.

5. How should BB’s therapy be monitored?
Monitor for drug efficacy:
• Frequency and intensity of attacks
• Anticipatory anxiety
• Sleep patterns
• Return to normal functional state

Monitor for drug adverse effects:
• Benzodiazepine = Sedation, ataxia, slurred speech, memory impairment, motor weakness, signs of dependence or abuse
• SSRI = Headache, diarrhea, nausea, irritability, sexual dysfunction, jitteriness

Monitor for medication adherence via interview with BB and checking SSRI refill patterns over time.

6. How should BB be counseled with respect to pharmacotherapy?
• Educate BB about the lag time between the start of drug therapy and the onset of therapeutic response with SSRI and that the benzodiazepine is for acute use only.
• Explain to BB the rationale for initiating treatment with lower doses (e.g., to avoid anxiogenic, CNS activation, or adverse GI effects). Counsel about the potential for sexual dysfunction and be encouraged to discuss this with her physician.
• Caffeine, OTC stimulants, nicotine, alcohol, ginseng, and drugs of abuse can exacerbate panic attacks so BB should be counseled to avoid these substances.
• BB should be made aware of the need to taper the SSRI and benzodiazepines (depending on the duration of therapy) when discontinuing them.
• If necessary, assist BB in finding qualified behavioral therapists, psychiatrists, patient support groups, and patient education materials.
• Educate BB on healthy lifestyle choices known to positively impact mental health, such as exercise, stress reducing techniques, balanced nutrition, and promote good sleep hygiene.

Principles of Good Sleep Hygiene
Practicing good sleep hygiene is necessary for all psychiatric patients. Poor sleep quality is both a consequence of and exacerbating factor for many psychiatric disorders. Pharmacy professionals should teach the following principles to patients:
1. Establish a routine time for bedtime and awakening.
2. Avoid daytime naps.
3. Avoid alcohol, caffeine, and CNS stimulants before bedtime.
4. Administer medications associated with insomnia in the morning.
5. Reduce ambient lighting at least one hour prior to bedtime.
6. Mask noises or use soft earplugs if necessary.
7. Exercise regularly, but not just prior to going to bed.
8. Use the bedroom only for sleeping, reading, or sex.
9. Avoid engaging in stressful activities, or unpleasant tasks near bedtime.
10. Limit fluid intake close to bedtime.
11. Avoid eating large meals immediately prior to bedtime.

### Strategies to Improve Adherence

#### Defining Medication Adherence Terms

**Compliance**
Compliance can be defined as the degree to which a patient’s actual dosing schedule corresponds with the regimen prescribed.

**Adherence**
Adherence can be defined as the right drug in the correct dose at the right interval.

**Persistence**
Persistence can be defined as success at seeing the medication therapy through to its intended point of closure.

#### Overview of Medication Adherence
The problem of poor medication adherence should be regarded as one of the most important public health issues. Improving adherence is challenging in underserved populations, where many examples of poor medication adherence exist.

Improving medication adherence is a critical factor toward generating favorable outcomes, and should be regarded as a shared responsibility of everyone in healthcare.

Generally, more emphasis and attention in previous years has been on medication access.

#### Prevalence of Medication Non-Adherence
Note: 50% of the 1.8 billion prescription medications dispensed annually in the United States are not taken correctly by patients.
Psychotropic Medication Adherence
Considerable time and resources are spent on making a proper diagnosis and initiating proper treatment. Costly patient work-ups, the extensive training of prescribers and pharmacists are to some degree “wasted” if patients do not adhere to their medications.

Many billions of dollars are spent on research and development of pharmaceuticals, as well as marketing expenditures, but the problem of adherence still persists.

An underlying assumption is often made that patients are adhering to their medications as prescribed.

Summary of Medication Adherence Studies 37-47

- Most adherence studies have been conducted in cardiovascular disease, diabetes, HIV, asthma, depression, and in special populations, such as elderly patients and ethnic minorities. Thus, extrapolating results of psychotropic medication adherence studies to the population at large is limited.
- Medication non-adherence rates are highest in those with:
  - Low socioeconomic status
  - Ethnic minorities
  - Low literacy rates
  - Patients who cannot properly identify their medications
- Similar rates of non-adherence have been found in rural communities and is also problematic in affluent populations.

Economic and Humanistic Toll of Non-Compliance 48

- About one-half of the prescriptions written annually are taken incorrectly by patients.
- Poor medication adherence is responsible for ~10% of all hospitalizations.
- Poor medication adherence is responsible for 23% of all nursing home admissions.
- Excessive treatments are associated with poor medication adherence, lost productivity, greater use of emergency care, and even premature deaths.
- The cost of non-adherence is $100-290 billion annually.

Test Yourself

Approximately 10% of hospital admissions are directly related to medication non-adherence.

A. True
B. False

The answer is A: True.
Measuring Medication Adherence 49-52

There is no gold standard for measuring medication adherence.

The use of APRNs, nurses, pharmacists and pharmacy technicians should be considered to improve medication reconciliation across patient care transitions as a method for improving adherence.

The use of both electronic health records, along with patient or caregiver/guardian interview are needed. Selection of the adherence measurement tool depends on multiple factors, including the type of intervention being evaluated, the resources of the organization, as well as ethical and legal considerations as related to patient intervention and confidentiality.

Morisky Medication Adherence Scale53-54

The Morisky Scale

The Morisky Scale is a four-item, self-reported adherence tool (1 point each):

1. Do you ever forget to take your medication?
2. Are you careless at times about taking your medication?
3. When you feel better do you sometimes stop taking your medication?
4. Sometimes if you feel worse when you take the medication, do you stop taking it?

This scale addresses barriers to taking medication. This also allows the healthcare provider to reinforce positive adherence behavior.

A score of >1 on the Morisky Scale requires further probing.
The Modified Morisky Scale
The Modified Morisky Scale can include two additional yes or no questions:

1. Do you know the long-term benefit of taking your medication as told to you by your doctor or pharmacist?
2. Sometimes do you forget to refill your medication on time?

The scale can be tailored for specific disease states and can help identify adherence problems, barriers, and potential solutions, as well as reinforce positive adherence behavior.

Patient-Reported Reasons for Non-Compliance

![Pie chart showing patient-reported reasons for non-compliance](image)

Test Yourself
The overall number one reason patients report for not taking their medication is that they cannot afford it.

A. True
B. False

The answer is B: False.
### Potential Barriers to Improving Adherence

<table>
<thead>
<tr>
<th>Poor attitude</th>
<th>Denial</th>
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<tbody>
<tr>
<td>Memory deficits</td>
<td>Fear or embarrassment</td>
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<tr>
<td>Language</td>
<td>Side effects</td>
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<td>Literacy</td>
<td>Religious beliefs</td>
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<td>Cultural beliefs</td>
<td>Unable to “see” results of drug therapy</td>
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<td>Alternative health beliefs</td>
<td>Lack of choices</td>
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<td>Poor support</td>
<td>Cost</td>
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<tr>
<td>Pride</td>
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</table>

### How and Why Do Patients Fail to Comply?

**Refusal to Take Medication**
- Patient not convinced of need for drug
- Fear of adverse/side effects
- Cost
- Dislike of taking drugs

**Discontinuation of Medication**
- Patient not convinced of drug’s benefit(s)
- Intolerance of adverse effects
- Patient cannot remember to take drug
- Cost

**Reducing Dosage to Less Than Prescribed**
- Patient not convinced of drug’s benefit(s)
- Intolerance of adverse effects
- Cost

**Increasing Dosage**
- Perception that more is better
- Perception that drug makes the patient feel good

Material Protected by Copyright
• To "hurry" the cure or treatment process

**Taking a Drug Holiday**

• Patient not convinced of drug's benefit(s)
• To achieve effect perceived as enjoyable
• To accommodate a transient life event
• Perception that drug interferes with certain events
• Inability to remember to take drug

**"White Coat" Compliance**

• Patient not convinced of drug's benefit(s)
• To procure approval from clinician or avoid rebuke

**Addressing Forgetfulness**

Knowing that patients report forgetfulness as a top reason for poor adherence, the following methods should be considered:

• Simplify prescribed regimens:
  - Once daily medications
  - Taper or discontinue potentially inappropriate medications

• Recommend the use of organizers and reminders:
  - Blister packs
  - Calendars
  - Dosage counters

• Consider using adherence-aiding strategies:
  - Reminders via phone calls and email
  - Medication diaries reviewed by healthcare provider

**Novel Approaches to Improve Medication Adherence**

• Automated refill reminder calls from community pharmacy
• Group patient education visits
• Use of technology:
  - Wireless electronic pill boxes
  - Text messages, PDA alarms, wristband alarms, and timers
  - “Glow cap” pill bottles
  - Comprehensive listing of devices: [www.epill.com](http://www.epill.com)
• Tools from American Society of Consulting Pharmacists:
  - [www.adultmedication.com](http://www.adultmedication.com)
• Pharmaceutical assistance programs:
  o http://www.pparx.org
• Nonprofit organizations providing medication assistance:
  o http://www.needymeds.org
  o http://www.rxoutreach.org

Reinforcing the Value of Medicines
It is important to educate the patient on the importance of taking medication as prescribed. Discuss what medication use can and cannot accomplish, set realistic goals, temper expectations, and provide clear indications of what may occur if the medication is not used properly or not at all.

Guard against making any statements that might undermine the relationship of a patient and his/her physician. Try to solve potential drug related problems without putting the patient in the middle by contacting the prescriber directly.

Nurses Can Improve Adherence
APRNs are most approachable and available, often “on-demand” and are ideally suited and positioned to provide feedback to prescriber on medication adherence.

APRNs have access to electronic health records and patient prescription profiles, and are trusted to provide accurate drug information.

Approach to Improving Medication Adherence
Before trying to improve medication adherence, the APRN should gather information that addresses the following concerns:

• Can the patient identify the medication?
• Does patient understand benefits of meds?
• Can the patient access the medication and select the right amount?
• Is the dosage form appropriate?
• Are any aids necessary for good compliance?
• What additional education is necessary for the patient and caregiver?
• What is the patient’s reading level? The reading level of drug information handouts for patient must be matched to the patient's educational level.

Strategies to Improve Medication Adherence

• Recall that health literacy does not equal intelligence.
• Do not assume that physicians have explained medication use to patients.

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• Avoid the use of medical verbiage and technical jargon.
• Even highly educated non-medical professionals have difficulty understanding medical terms.
• Ask patient to repeat instructions (teach-back method).
• Keep directions and labels simple, use fewer medical terms.
• Emphasize importance of medication adherence at each encounter with patient.
• Involve the patient’s spouse or other immediate family members or guardian.

Assess and Remove Adherence Barriers
• Assure patients that they will be an integral part of their own therapy and will have choices to make. Simplify drug regimen as much as possible, and accommodate the needs of physically handicapped patients.
• Provide pill keepers and calendars for patients with minor memory problems.
• Utilize language interpreters where necessary.
• Ask about transportation for picking up medication and arrange for prescription delivery where available.

Establish Trust
✓ Build relationship with patient.
✓ Be available and approachable.
✓ Assess the patient’s willingness to learn from you.
✓ Be sincere and honest.
✓ Express a desire for patient to get well and maintain quality of life.
✓ Use a positive approach and exhibit confidence in patient and treatment plan.
✓ Recall that past behavior is a good predictor of future adherence.

Conclusion
By addressing patients’ adherence issues and focusing on the value of their medicines, APRNs can make a significant difference in patients’ healthcare outcomes!

References


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