General Psychiatry

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GENERAL PSYCHIATRY

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Learning Objectives

1. Describe pharmacotherapeutic options for managing major depression, bipolar disorder, schizophrenia, anxiety disorders, insomnia, and substance abuse.
2. Describe the drugs used to treat these disorders with respect to unique pharmacologic properties, therapeutic uses, adverse effects, and cognitive and behavioral effects.
3. Formulate a pharmacotherapeutic treatment plan when presented with a patient having major depression, bipolar disorder, schizophrenia, anxiety disorder, insomnia, or substance abuse.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A.B. is a 25-year-old woman who presents to your practice with a depressed mood that has worsened over the past few weeks. She struggles to get out of bed in the morning. When she is not sleeping she is eating. She has gained 10 lb in the past month. She is worried about her job and does not feel like she is “pulling her weight,” even though she recently received a glowing evaluation. She has passive thoughts of harming herself but no definite plan. Her past medical history includes anxiety, gastroesophageal reflux disease, and hypothyroidism. She currently takes levothyroxine 100 mcg daily, lansoprazole 30 mg every morning, and alprazolam 0.5 mg three times daily for anxiety. Which medication would best treat her symptoms?
   A. Desipramine.
   B. Fluoxetine.
   C. Mirtazapine.
   D. Paroxetine.

2. K.M. is a 56-year-old woman with recurrent major depression, diabetes type 2 with newly diagnosed neuropathy, obesity, and coronary artery disease. She is currently taking citalopram 40 mg daily, carvedilol 25 mg twice daily, lisinopril 40 mg daily, and metformin 1000 mg twice daily. She is tearful during her appointment and continues to have symptoms of depression despite initial improvement on citalopram. She wants to switch antidepressants. Which would be most beneficial?
   A. Bupropion.
   B. Duloxetine.
   C. Nortriptyline.
   D. Sertraline.

3. L.O. is a 45-year-old man who presents agitated and sweating. His right eyelid started twitching about 1 hour ago, and he cannot get it to stop. He developed cold symptoms 2 days ago and began taking dextromethorphan and pseudoephedrine. His past medical history includes depression, hypertension, and hyperlipidemia. He takes paroxetine 40 mg at bedtime, diltiazem XR 240 mg daily, and rosuvastatin 10 mg daily. Which combination of medications is contributing to his current symptoms?
   A. Cetirizine and paroxetine.
   B. Dextromethorphan and pseudoephedrine.
   C. Diltiazem and pseudoephedrine.
   D. Paroxetine and dextromethorphan.

4. H.G. is a 31-year-old man with a 5-year history of bipolar disorder type I, for which he takes lithium 300 mg twice daily. His serum concentration, taken yesterday before his morning dose of lithium, is 1.0 mEq/L. He has been without manic symptoms for the past few years. He was admitted for a suicide gesture using acetaminophen. Over the past few weeks, he has lost interest in his job and is isolating himself from other people. Which medication would best help his acute symptoms?
   A. Aripiprazole.
   B. Lamotrigine.
   C. Quetiapine.
   D. Venlafaxine.

5. H.K. is a 28-year-old woman with a history of bipolar type I. She takes lithium 450 mg twice daily. Her last serum concentration (3 months ago) was 0.7 mEq/L. She presents today for an annual examination. Her laboratory test results include sodium 138 mEq/L, potassium 4.7 mEq/L, serum creatinine concentration 0.9 mg/dL, glucose 124 mg/dL, and thyroid-stimulating hormone 24 U/mL. She is 61 inches tall, and she weighs 165 lb, 15 of which
she has gained in the past 2 months. Additional medications include olanzapine 10 mg at bedtime, Yasmin daily, and a multivitamin. Which of the following accounts for these findings?

A. Hypothyroidism.
B. Lithium concentration.
C. Olanzapine.
D. Yasmin.

6. I.T. is a 43-year-old woman with rapid-cycling bipolar disorder, hypertension, obesity, and asthma. She recently switched from lithium to divalproex sodium 500 mg daily. She additionally takes lamotrigine 150 mg twice daily, aripiprazole 30 mg daily, ramipril 10 mg daily, albuterol HFA 2 puffs every 6 hours, and Advair 250/50 twice daily. She started a prednisone taper 3 days ago for an asthma exacerbation. Today she presents with abdominal pain with rebound tenderness, nausea, and vomiting. Laboratory test results include sodium 141 mEq/L, potassium 3.3 mEq/L, chloride 95 mEq/L, carbon dioxide 26 mmol/L, serum creatinine concentration 1.0 mg/dL, glucose 72 mg/dL, cholesterol 165 mg/dL, triglycerides 188 mg/dL, aspartate aminotransferase (AST) 27 IU/L, alanine aminotransferase (ALT) 21 IU/L, amylase 456 U/L, and lipase 387 U/L. Which medication is responsible for the current clinical picture?

A. Aripiprazole.
B. Divalproex sodium.
C. Lamotrigine.
D. Prednisone.

7. N.B. is a 36-year-old man with 16-year history of schizophrenia. He was recently switched to aripiprazole from haloperidol because of gynecomastia and impotence. Today he is pacing your office. He seems anxious and agitated. He has not been sleeping well and feels uncomfortable in his skin. Which medication would help relieve his symptoms?

A. Benztropine.
B. Dantrolene.
C. Lorazepam.
D. Propranolol.

8. T.Y. is a 64-year-old woman with a 25-year history of schizophrenia. Over the past year she has developed involuntary chewing motions and abnormal blinking. It has begun interfering with her ability to eat. She is currently taking haloperidol 2.5 mg twice daily. Her symptoms improved when her haloperidol dose was decreased from 5 mg twice daily but have not resolved. She wants to switch antipsychotics. Which would offer the most relief from her symptoms?

A. Chlorpromazine.
B. Clozapine.
C. Quetiapine.
D. Risperidone.

9. U.M. is a 38-year-old woman with a 4-year history of schizophrenia. Within the past year she has been diagnosed with diabetes type 2 and dyslipidemia. Her body mass index is 32 kg/m². Her father died of a myocardial infarction (MI) at age 42. She has been treated with risperidone but has developed galactorrhea. Concomitant medications include atorvastatin, metformin, and liraglutide. Which antipsychotic would be the best choice?

A. Olanzapine.
B. Paliperidone.
C. Quetiapine.
D. Ziprasidone.

10. N.Y. is a 20-year-old woman who presents to the emergency department after experiencing trembling, sweating, chest pain, and shortness of breath accompanied by intense fear. An MI has been ruled out. Which medication regimen would effectively treat her acute symptoms?

A. Alprazolam.
B. Buspirone.
C. Hydroxyzine.
D. Paroxetine.

11. T.R. is a 55-year-old woman with generalized anxiety disorder. Concomitant medical conditions include history of breast cancer, dyslipidemia, osteoarthritis, menopausal symptoms, and osteopenia. She takes tamoxifen, simvastatin, ibuprofen, lorazepam, and alendronate. Her physician would
like her to have better control of her anxiety symptoms. He would also like to taper her off lorazepam. Which agent would be the best choice?
A. Bupropion.
B. Fluoxetine.
C. Pregabalin.
D. Venlafaxine.

12. O.P. is a 74-year-old woman who has difficulty getting to sleep. Once she falls asleep she rests comfortably throughout the night. She struggles with keeping a bedtime. This problem has been ongoing for the past few months. She has no contributing factors. Concomitant medical conditions include hypertension, arthritis, and mild cognitive impairment. She has tried diphenhydramine. She states it helped for only a few nights and “it made me loopy.” She would like a medication with the least risk of hangover effect. Which medication is best?
A. Eszopiclone.
B. Ramelteon.
C. Suvorexant.
D. Zolpidem.

13. M.K. is a 23-year-old man with a history of heroin addiction. He has been successfully maintained on methadone 40 mg daily for 1 year. He would like an option that does not require him to go to a daily opioid treatment program to get his methadone dose. He is not taking other medication, nor does he abuse other substances. Which treatment regimen is appropriate?
A. Initiate supervised buprenorphine/naloxone.
B. Switch to buprenorphine x 2 days, then buprenorphine/naloxone.
C. Switch to naltrexone.
D. Taper to methadone 30 mg, then switch to buprenorphine.

14. C.H. is a 55-year-old man with a 30-year history of alcohol dependence. He drinks 1 pint of vodka daily. He has tried numerous times to quit without success. He has recently reconciled with his estranged son and wants to be sober so that he can be more present in his son’s life. His liver function test results include AST 143 IU/L, ALT 74 IU/L, albumin 4.0 g/dL, alkaline phosphatase 75 IU/L, total bilirubin 0.3 mg/dL, prothrombin time 0.9 seconds, platelet count 370 x 10^3 cells/mm^3, and creatinine clearance 40 mL/min. After detoxification, which maintenance treatment is appropriate?
A. Acamprosate 666 mg three times daily.
B. Chlordiazepoxide 25 mg four times daily.
C. Disulfiram 500 mg daily.
D. Naltrexone 50 mg daily.

15. J.Z. is a 44-year-old man who is getting ready to be discharged from the hospital after an MI. He has a 25-pack-year history of smoking cigarettes and smokes 1-1/2 packs per day. He has tried twice unsuccessfully to quit. His additional past medical history includes recurrent depression. He tried quitting cold turkey the first time about 5 years ago. He resumed smoking 6 months later when he lost his job. He tried again approximately 6 months ago using nicotine gum. He used the 2-mg strength. To save money, he chewed 7 pieces daily. Which regimen would be best?
A. Bupropion.
B. Nicotine 4 mg gum.
C. Nicotine patch 21 mg/day.
D. Varenicline.
Patient Cases

Questions 1–4 pertain to the following case:

A.Z. is a 45-year-old woman with sleep apnea, hypertension, type 2 diabetes mellitus, and chronic pain. She is being seen in the clinic today for an assessment of her depressive symptoms and medication evaluation. She endorses sad mood, poor appetite (lost 15 lb), poor concentration, and feelings of hopelessness and worthlessness for the past 3 weeks. She has also stopped going to her book club because she is not motivated to get out of the house, and she has frequent nocturnal awakening. She denies suicidal or homicidal ideation. She denies any use of alcohol, tobacco, or illicit drugs. She is currently taking hydrochlorothiazide, metformin, hydrocodone/acetaminophen, and aspirin. You decide that A.Z. should receive an antidepressant in the selective serotonin reuptake inhibitor (SSRI) class to treat her depressive symptoms.

1. Which SSRI would be most likely to interact with her current medications?
   A. Citalopram.
   B. Fluvoxamine.
   C. Paroxetine.
   D. Sertraline.

2. Which antidepressant would be most appropriate for A.Z.’s depressive symptoms?
   A. Bupropion.
   B. Fluoxetine.
   C. Mirtazapine.
   D. Venlafaxine.

3. It has been 4 weeks since A.Z.’s initial visit with you, and she has been treated with citalopram 20 mg/day in the morning. She still presents with sad mood, but her insomnia, concentration, and appetite have improved. She still has feelings of hopelessness and worthlessness, lack of motivation, and anhedonia. At this point, which is the best recommendation to optimize her therapy?
   A. Continue at current dose of 20 mg/day.
   B. Increase the current dose to 40 mg/day.
   C. Add bupropion 150 mg twice daily.
   D. Switch to a different SSRI.

4. Six months later, A.Z. reports that although her depression symptoms have resolved, she has “trouble” during intercourse, which is quite disturbing to her. You determine that she has anorgasmia caused by citalopram treatment. Which is the most appropriate recommendation at this time?
   A. Discontinue citalopram.
   B. Add bupropion to treat anorgasmia.
   C. Switch to a different SSRI.
   D. Switch to mirtazapine.
I. DEPRESSION

A. Identification of Depressive Disorders. This overview is based on the *Diagnostic and Statistical Manual for Mental Disorders (DSM-5)*; please consult the DSM-5 for complete diagnostic criteria.

1. Major depressive disorder (MDD), otherwise called unipolar disorder. It is diagnosed when a patient exhibits at least 5 of the following symptoms nearly every day for at least 2 weeks:
   a. The patient must have a depressed mood or anhedonia (loss of interest in pleasurable activities).
   b. Additional symptoms include sleep disturbances, changes in weight or appetite, decreased energy, feelings of guilt or worthlessness, psychomotor retardation or agitation, decreased concentration, and suicidal ideation.
   c. The symptoms must interfere with the patient’s everyday ability to function.

2. Persistent depressive disorder (dysthymia): Chronic depressed mood occurring more days than not for at least 2 years but does not meet the criteria for MDD

B. Assessment of Patients With MDD

1. Psychiatric history: A thorough history of symptoms is compared with the diagnostic criteria, and the diagnosis is made from the collected data.

2. Clinician rating scales: These are psychometric instruments used to identify depression and assess its severity. Common examples are the Hamilton Rating Scale for Depression (HAM-D) and the Quick Inventory of Depressive Symptoms Clinician Rated. A response is usually defined as at least a 50% reduction in the HAM-D score. “Remission” is a return to a normal state or a HAM-D of 7 or less. Scores from these scales are not required for the diagnosis, but the HAM-D is a standard instrument used to show efficacy in clinical trials for U.S. Food and Drug Administration (FDA) approval. The Clinical Global Impression scale is a clinician-rated scale that evaluates the severity and improvement of patients overall. The Montgomery-Åsberg Depression Rating Scale is another instrument that evaluates symptoms of depression. The Patient Health Questionnaire–9 is based on the DSM-5 diagnostic criteria for major depression. It is easily administered and assessed and is thus frequently used in the primary care setting.

3. Patient rating scales: These are patient-completed rating instruments. Answers to the questions are used to identify and assess the level of depression. The Beck Depression Inventory and the Quick Inventory of Depressive Symptoms Self-Rated are examples.

4. Physical examination and laboratory tests: These are necessary to rule out physical causes (e.g., thyroid disorders, vitamin deficiencies) that may mimic symptoms of depression.

5. Biologic testing: Depression is commonly associated with abnormalities in the dexamethasone suppression test and tests of the thyroid axis. However, these tests are not routinely used in clinical practice.

6. Medications and substances (e.g., interferons, benzodiazepines, barbiturates, alcohol, central nervous system depressants, lipid-soluble β-blockers, withdrawal from stimulants, cocaine, amphetamines) can have depression as an adverse effect. Pharmacists should perform a medication and substance use review to identify possible causes.

C. Therapeutic Options

1. Psychotherapy and exercise: Examples include interpersonal psychotherapy and cognitive-behavioral therapy (CBT). With psychotherapy, it takes longer to observe effectiveness, but when combined with pharmacotherapy, it is effective. It may have broader and longer-lasting effects. Psychotherapy is recommended as monotherapy as initial treatment in patients with mild to moderate MDD (CBT and interpersonal therapy have the best evidence).

2. Pharmacotherapy: Medication therapy may lead to a more rapid response than psychotherapy, but when it is discontinued, there is a risk of relapse and adverse effects.
3. Electroconvulsive therapy (ECT): Option for refractory depression, depression in pregnancy, psychotic depression, and other conditions for which medications may not be optimal or effective. The usual cycle is two or three treatments per week. Temporary memory loss is common, and medications that affect seizure threshold must be withdrawn before treatment. Electroconvulsive therapy has also been recently suggested as initial treatment if symptoms are severe or life threatening (American Psychiatric Association [APA] 2010 guidelines).

D. Pharmacotherapeutic Options: Considerations and Keys to Use
1. Selection: All antidepressants are considered to be equally efficacious. First-line medications include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine. Consider possible drug-drug and drug-disease interactions, concurrent illnesses, prior responses, family members’ prior responses, patient preference, and cost.
2. Onset: In general, it takes 4–6 weeks to see the full effect of antidepressants, given the correct drug, dose, and adherence, but it may take as long as 8 weeks to see a response. Remission may take up to 12 weeks. Some symptoms (e.g., sleep disturbances) may show improvement in 1–2 weeks.
3. Adequate trial: An adequate trial includes the correct drug for the patient and a therapeutic dose for an appropriate duration. A therapeutic trial ranges from 4 to 8 weeks (2010 APA practice guideline).
4. Response and remission: A response is usually defined as a 50% reduction in symptoms. Remission is a return to normal mood (e.g., HAM-D of 7 or less). Optimizing the dose or duration is important for achieving remission.
5. Efficacy of antidepressants according to rigorous clinical trials is about 60%–70%, regardless of drug. Effectiveness, which is more reflective of clinical practice, is lower, about 50%–60%. The remission rate with one antidepressant is about 30%, seen in the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D trial), when the first drug is initiated.
6. Drug interactions (Table 1): Many antidepressants inhibit cytochrome P450 (CYP) enzymes.

Table 1. Antidepressants and the CYP System

<table>
<thead>
<tr>
<th>CYP Enzyme</th>
<th>Inhibition Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Fluvoxamine: high</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine: moderate</td>
</tr>
<tr>
<td>2C</td>
<td>Fluoxetine, fluvoxamine, sertraline: low</td>
</tr>
<tr>
<td>2D6</td>
<td>Fluoxetine, paroxetine: very high</td>
</tr>
<tr>
<td></td>
<td>Duloxetine: moderate</td>
</tr>
<tr>
<td></td>
<td>Bupropion, citalopram, escitalopram, sertraline: very low</td>
</tr>
<tr>
<td>3A4</td>
<td>Nefazodone: very high</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine: moderate</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine: low</td>
</tr>
<tr>
<td></td>
<td>Sertraline: very low</td>
</tr>
<tr>
<td>Minimal CYP inhibition</td>
<td>Venlafaxine, desvenlafaxine, mirtazapine, levomilnacipran</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450.

E. Tricyclic Antidepressants
1. Tricyclic antidepressants (TCAs) were the first antidepressants available. They are seldom used for depression, but they have several off-label uses such as treatment for pain syndromes, migraine prophylaxis, and anxiety disorders. They are effective, but adverse effects have limited their use. Now that newer agents with more tolerable adverse effect profiles are available, these agents are used less often.
2. They block the reuptake of serotonin and norepinephrine (NE). The tertiary amines are more potent for NE uptake and are metabolized to active secondary amines.

3. In addition to serotonin and NE reuptake, TCAs have α-adrenergic blockade, antihistaminic effects, and anticholinergic effects, leading to orthostasis, sedation, and anticholinergic symptoms, respectively. They also have cardiotoxic effects (Table 2).

4. TCAs can be fatal in overdose. They cause seizures and torsades de pointes. An actively suicidal patient should not receive a TCA.

Table 2. Adverse Effect Profile of the Commonly Used Tricyclic Antidepressants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anticholinergic</th>
<th>Sedation</th>
<th>Orthostatic Hypotension</th>
<th>Cardotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tertiary amines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td><strong>Secondary amines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desipramine</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

5. These drugs must be used cautiously in patients with cardiac disease or seizure disorders. Patients at risk of orthostatic hypotension are at elevated risk of falls if they take these agents, and appropriate caution should be taken.

6. One advantage of TCAs is that therapeutic serum concentrations can be measured. Therapeutic levels can be used to confirm adherence or toxicity. In clinical practice, this is an infrequent practice.

7. A withdrawal syndrome occurs if these drugs are discontinued too quickly. Symptoms reflect the reversal of anticholinergic effects and include lacrimation, nausea, and diarrhea, with insomnia, restlessness, and possible balance problems. Gradual dose reductions help reduce these symptoms.

F. Monoamine Oxidase Inhibitors

1. Monoamine oxidase inhibitors (MAOIs) block the enzyme responsible for the breakdown of certain neurotransmitters, such as NE. There are two forms of this enzyme (MAO-A and MAO-B), and drugs can block one or both of them. They are effective antidepressants and may be especially useful for atypical depression (hypersomnia, hyperphagia, and mood reactivity).

2. Nonselective drugs (phenelzine and tranylcypromine) are available in the United States.

3. Patients taking MAOIs must be educated and monitored to avoid foods high in tyramine (e.g., aged cheese, preserved meats) because of the potential for precipitating a hypertensive crisis. A dietary consultation can be helpful in this respect.

4. Drug interactions with MAOIs are considerable and include over-the-counter decongestants, antidepressants, stimulants, antihypertensives, and others. When switching a patient from another antidepressant to an MAOI, it is prudent to wait 2 weeks after the antidepressant is discontinued before initiating the MAOI (except for fluoxetine, in which case the waiting period should be 5–6 weeks). When a patient is changed from an MAOI to another antidepressant, a 2-week washout period is usually adequate.

5. Selegiline (MAO-B inhibitor) is available in a patch formulation called Emsam for the treatment of depression. It is available in doses of 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours. Once the dose reaches 9 mg/24 hours, an MAOI diet is required. How this drug compares with other antidepressants remains unknown.
G. Selective Serotonin Reuptake Inhibitors (SSRIs)

1. SSRIs selectively inhibit the reuptake of serotonin into the presynaptic neuron. There has been speculation that they also desensitize the presynaptic serotonin autoreceptor involved in the negative feedback loop that normally inhibits serotonin release. Whichever is true, the result is increased serotonin concentrations in the synapse. The FDA has approved six SSRIs for the treatment of depression: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. Fluvoxamine is indicated only for obsessive-compulsive disorder (OCD) but is an effective antidepressant.

Table 3. Characteristics of SSRIs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
<th>Paroxetine</th>
<th>Fluvoxamine</th>
<th>Citalopram</th>
<th>Escitalopram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>1–4 days</td>
<td>26 hours</td>
<td>21 hours</td>
<td>15 hours</td>
<td>32 hours</td>
<td>27–32 hours</td>
</tr>
<tr>
<td>Active metabolite</td>
<td>Yes(^b)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Usual dose (mg/day)</td>
<td>20–60</td>
<td>50–200</td>
<td>10–60</td>
<td>50–300</td>
<td>20–40</td>
<td>10–20</td>
</tr>
<tr>
<td>Maximal daily dose (mg)</td>
<td>80</td>
<td>200</td>
<td>50</td>
<td>300</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^a\)Indicated only for obsessive-compulsive disorder; seldom used for depression.

\(^b\)Norfluoxetine.

SSRI = selective serotonin reuptake inhibitor.

2. The efficacy of SSRIs is equal for treatment of depression. There are slight differences in adverse effect profiles, and patients may tolerate one better than another. The STAR*D trial showed that patients who do not respond to one SSRI may respond to another.

3. Blockade of serotonin reuptake leads to an increase in serotonin overall and may influence all subtypes of serotonin receptors. Some of these (serotonin-2A, serotonin-2C, serotonin-3, and serotonin-4) may be responsible for some of the unwanted adverse effects (e.g., insomnia, restlessness, gastrointestinal [GI] complaints). Activation, agitation, anxiety, or panic may be seen in some patients, especially during the early phase of therapy. The most common adverse effects associated with this class of agents include GI complaints, insomnia, restlessness, headache, and sexual dysfunction. In general, the most activating SSRIs are fluoxetine, sertraline, and vilazodone, whereas paroxetine and fluvoxamine are the most sedating. Vortioxetine, citalopram, and escitalopram do not have appreciable sedating or activating effects. Sexual dysfunction is more common than reported in the prescribing information. Some interventions to consider for SSRI-induced sexual dysfunction include using the wait-and-see method, adding bupropion for the treatment of sexual dysfunction, lowering the dose of the SSRI, or adding an agent such as sildenafil or cyproheptadine. Of course, changing to a drug less likely to cause this problem is also reasonable.

4. Because these drugs have such potent serotonergic activity, combinations with other drugs affecting serotonin can lead to serotonin syndrome. Examples include MAOIs, dextromethorphan, meperidine, sympathomimetics, triptans, lithium, TCAs, and SNRIs. Serotonin syndrome includes symptoms from three clusters: neuromuscular hyperactivity (e.g., myoclonus, rigidity, tremors, incoordination), altered mental status (agitation, confusion, hypomania), and autonomic instability (hyperthermia, diaphoresis). It can be subtle in onset or be confused with neuroleptic malignant syndrome. Treatment includes discontinuing the offending agent, providing supportive measures such as cooling blankets and respiratory assistance, and providing clonazepam for myoclonus, anticonvulsants for seizures, and nifedipine for hypertension.
5. SSRIs have been associated with extrapyramidal symptoms (EPS), including akathisia, dystonia, and bradykinesia, but these are not common. This appears to result from an effect of serotonin on dopaminergic neurotransmission in the basal ganglia.

6. A withdrawal syndrome has been observed, especially for the drugs with shorter half-lives, so a gradual dose reduction (e.g., over 2–4 weeks) may be indicated. Symptoms include flulike symptoms, such as nausea and chills, and neurologic symptoms, such as paresthesias, insomnia, anxiety, and “electric shock”-type sensations. If the problem is severe or persists, the drug can be reinitiated and the dose gradually reduced again. It is most common with paroxetine, less so with sertraline, and even less likely with fluoxetine.

7. In 2001, the FDA ordered changes to citalopram package labeling limiting the daily dose to a maximum of 40 mg because of an elevated risk of QTc prolongation at daily doses greater than 40 mg. Patients who have risk factors for QTc prolongation (congenital long QTc syndrome, bradycardia, hypokalemia, hypomagnesemia, recent acute myocardial infarction, and uncompensated heart failure) or have concomitant medications that may increase QTc interval should not be treated with citalopram. Doses of citalopram should be lowered to 40 mg/day in patients who are receiving higher dosages unless the benefits significantly outweigh the risks. The maximal recommended dose of citalopram is 20 mg/day for patients with hepatic impairment, patients who are older than 60 years, patients who are CYP2C19 poor metabolizers, or patients who are taking concomitant cimetidine or another CYP2C19 inhibitor.

8. These drugs are not as lethal in cases of overdose as are TCAs. All SSRIs are available in generic form except for vilazodone and vortioxetine. The low cost and better tolerability of SSRIs warrant them as first-line treatment of MDD in most patients.

9. Extended dosing formulations: Fluoxetine 90 mg can be taken once weekly. It is taken only during continuation therapy rather than as initial treatment. Paroxetine controlled release may have lower rates of nausea in the first week of treatment; efficacy is comparable, and both formulations are administered once daily. The weekly and controlled release (CR) products are available generic but are higher in cost.

10. Escitalopram is the S-isomer of citalopram. It is the active component of the racemic mixture. At a 10-mg dose, it is as effective as citalopram 20 mg (or 40 mg as described in prescribing information), but at this dose, there are fewer adverse effects. At higher doses, this advantage is not as pronounced.

11. SSRIs appear to increase the risk of bleeding. Several mechanisms have been proposed, including the inhibition of serotonin activation of platelets. Case-control and cohort studies also suggest an elevated incidence of both vertebral and nonvertebral bone fractures.

H. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

1. Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran block the reuptake of NE and serotonin. Unlike TCAs, they have negligible effects at other receptors that cause anticholinergic or antihistaminic adverse effects, with the possible exception of duloxetine, which appears to have a slightly higher incidence of anticholinergic symptoms. Venlafaxine has a dose-related effect on NE compared with desvenlafaxine and duloxetine. At doses less than 150 mg/day, venlafaxine has primarily a serotonin effect.

2. Levomilnacipran is a newly approved SNRI. It is the enantiomer of milnacipran, the latter of which is approved for the treatment of fibromyalgia but not depression. Levomilnacipran is not approved for the treatment of fibromyalgia. The dose must be adjusted in renal insufficiency, and its use is not recommended in end-stage renal disease. Levomilnacipran can cause hyponatremia and increase bleeding risk. The capsule should not be crushed or opened. It is metabolized through CYP3A4 (major pathway) and through CYP2C19 and CYP2D6, among others (minor pathways). Monitor signs and symptoms of potential toxicities if CYP3A4 inhibitors are used concomitantly. Both blood pressure elevations and orthostatic hypotension can occur. It is a more potent inhibitor of NE than venlafaxine or duloxetine (NE slightly preferred to serotonin).
3. Whether the dual action of venlafaxine makes it more effective than SSRIs is an area of continued research. There appear to be patients (e.g., treatment nonresponders) who benefit either from agents that affect NE and serotonin or from combinations of drugs with that effect.

4. The adverse effect profile of venlafaxine is similar to that of the SSRIs, with GI complaints being common. Of note, venlafaxine can cause increases in blood pressure, which are usually mild and not clinically significant unless the patient already has hypertension that is not well controlled. This is a dose-related phenomenon, as described earlier. All the SNRIs may produce serotonin syndrome. In overdose situations, both duloxetine and venlafaxine have been associated with higher rates of death compared with SSRIs. The risk of suicide completion with SNRIs is still lower than with TCAs.

5. Duloxetine has also been approved for the treatment of diabetic peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain caused by chronic lower back pain or osteoarthritis pain. Be careful when using this drug with CYP2D6 inhibitors. Monitor blood pressure, because increases have been observed. This drug can cause liver toxicity and should not be used in patients with hepatic insufficiency, end-stage renal disease requiring dialysis, or severe renal impairment.

6. Abrupt discontinuation of venlafaxine can lead to a withdrawal syndrome similar to that with the SSRIs.

7. Desvenlafaxine (Pristiq) is an active metabolite of venlafaxine. Whether it has any advantage over the parent compound is controversial.

8. Both desvenlafaxine and levomilnacipran doses must be adjusted downward with decreased renal function.

I. Mixed Serotonergic Medications

1. Vilazodone (Viibryd) is an SSRI with partial agonist at the serotonin-1A receptor. The clinical significance of this effect is unknown. It has a half-life of 25 hours but does not have active metabolites. Both the usual and maximum doses are 40 mg daily.

2. Vortioxetine inhibits serotonin reuptake, but its pharmacologic profile differs from that of other SSRIs. It has additional agonist activity at the serotonin-1A receptor, partial agonist activity at the serotonin-1B receptor, and antagonistic activity at the serotonin-3, serotonin-1D, and serotonin-7 receptors. The clinical significance of vortioxetine’s effect on the serotonin receptors is currently unknown, but it also appears to improve measures of cognitive function that appear independent of its antidepressant effects. Vortioxetine has a half-life of 66 hours and no active metabolites. The starting and usual dose is 10 mg daily, with a maximum daily dose of 20 mg. It is metabolized by CYP2D6, and the maximal dose for poor metabolizers or patients taking a strong CYP2D6 inhibitor is 10 mg daily.

3. Trazodone is a serotonin reuptake inhibitor that also blocks serotonin-2A receptors. It does not cause anticholinergic or cardiotoxic effects, as the TCAs do, but it still causes orthostatic hypotension and sedation. Because of its sedative properties, trazodone is often used for insomnia but at lower doses than those used to treat depression. It is important to be aware of the potential for priapism, even though it is rare (0.1% or less).

4. Nefazodone is a relative of trazodone with some pharmacologic differences. It, too, is a serotonin-2A antagonist, but it also blocks the reuptake of serotonin and NE. Some have referred to this class as serotonin antagonist reuptake inhibitors (serotonin-2A antagonist/reuptake inhibitors). Unlike trazodone, it causes minimal effects on sexual function and is less likely to cause orthostatic hypotension. Some data suggest that the serotonin-2A–blocking activity makes this drug more effective for anxiety associated with depression. The short half-life makes it necessary to administer doses twice daily. The most common adverse effects of this drug include sedation, GI complaints, dry mouth, constipation, confusion, and light-headedness. Because it is a potent inhibitor of CYP3A4, caution is necessary when it is used concomitantly with drugs metabolized by this system. Because of the potential for liver toxicity and the black box warning, nefazodone is now considered a second- or third-line agent. Liver function tests must be monitored if nefazodone is used. The branded product has been withdrawn from the market. Generics remain available.
5. Mirtazapine is an antagonist of presynaptic $\alpha_2$-autoreceptors and heteroreceptors, which results in an increase in NE and serotonin in the synapse. In addition, the drug blocks serotonin-2A (resulting in no sexual dysfunction, no anxiety, and sedation), serotonin-3 (no nausea and no GI disturbances), and serotonin-2C (weight gain) receptors. Although the drug is better tolerated than the TCAs, it still has a pronounced sedative effect, together with increased appetite, weight gain, constipation, and asthenia. Abnormal liver function tests may occur, and there appears to be a very small risk of neutropenia or agranulocytosis. Lower doses may be sedating, whereas higher doses may cause insomnia.

J. Bupropion
1. This drug is primarily an inhibitor of dopamine and NE reuptake (at high doses), with minimal effects on serotonin. Its exact mechanism of action remains to be defined. The parent drug blocks dopamine reuptake, whereas the metabolite blocks NE reuptake.
2. The most important adverse effect is increased risk of seizures. This risk can be minimized by the following:
   a. Avoid use in susceptible patients (e.g., history of seizure disorder, eating disorders).
   b. Do not give more than 150 mg/dose or 450 mg/day (immediate release), 400 mg/day (sustained release), or 450 mg/day (extended release).
   c. Avoid dosage titration any more frequently than every 4 days for sustained or extended release and every 3 days for immediate release.
   d. The sustained- and extended-release products may also cause fewer adverse effects; they have largely replaced the immediate-release tablets.
3. The most common adverse effects include insomnia, anxiety, irritability, headache, and decreased appetite. The drug can also increase energy and cause psychosis. As noted previously, the drug may actually improve sexual function; thus, it may be useful in patients not tolerating other agents for this reason. Bupropion has also been used for attention-deficit/hyperactivity disorder and may help with concentration.

K. Antidepressants and Suicidality: Antidepressants have been associated with an increased risk of suicidal thinking and behaviors, particularly in children, adolescents, and young adults (up to 24 years of age), which has resulted in a black box warning for all antidepressants, both older and newer agents. It is important to monitor patients, especially children and adolescents, for treatment failure or worsening symptoms of depression when these drugs are initiated or the dose is increased. Other signs to watch for include suicidal ideation, agitation and anxiety (activation syndrome), and other symptoms that are unlike the presenting symptoms of depression in the patient. A medication guide must be distributed before antidepressants are dispensed.

L. Initiating, Adjusting, and Monitoring Therapy
1. There are three phases of therapy:
   a. Short term (acute): The goal of this phase is remission, which may take 12 weeks. Remission is defined as at least 3 weeks with no symptoms of depressed mood and anhedonia and no more than 3 remaining symptoms of depression.
   b. Continuation: The goal of this phase is to keep the symptoms in remission by using full-dose therapy. This phase usually continues for 4–9 additional months to keep the patient in remission.
   c. Maintenance: Long-term therapy at full doses may be required in patients at high risk of relapse, which would include prior episodes of depression or a strong family history of relapse. The duration of this phase is determined on an individual basis.
2. An adequate trial of any agent includes full therapeutic doses for at least 6 weeks, up to 12 weeks. If there is no response at this point, the drug can be considered a failure.
3. When one drug has failed, another agent from another class is often tried. However, some patients who do not respond to one SSRI may respond to another, and this is a reasonable option. Treatment resistance can usually be considered when two or more agents from different classes have been tried. At this point, ECT, augmentation therapy, or combination therapy can be considered, if they have not been used already.

4. Patients should be monitored for response through interviews or by repeating rating scales. In addition, patients (and their support systems, if available) should receive education about therapy and be closely monitored for adverse effects. Although most of the adverse effects are not life threatening, they do have an important effect on adherence.

5. The FDA has required that package labels for antidepressants include a statement to monitor patients for emerging suicidal thoughts and behaviors and continuing depressed mood, especially when antidepressants are initiated.

M. Antidepressant Combination Therapy

1. Drugs with different pharmacologic actions are available, and as more is learned about depression, it may be advantageous to treat different systems selectively. It is now possible to affect serotonin, NE, and dopamine differentially. Researchers are actively looking at specific symptoms of depression to determine whether certain presentations respond better to an agent that affects certain neurotransmitter systems. At this point, data are insufficient to guide treatment, but it can be expected that combinations will be used, especially for treatment-resistant depression.

2. The use of combinations with lower doses of each may lead to fewer adverse effects.

3. Using a second antidepressant may offset an adverse effect of another (e.g., using trazodone to treat SSRI-induced insomnia).

4. Adding bupropion to existing SSRI therapy is a strategy for patients who do not fully respond to the SSRI alone.

N. Augmentation Therapy

1. Patients not responding adequately have been successfully treated when nonantidepressant drugs are added to augment existing antidepressant therapy. Data indicate that many patients will respond when these agents are used.

2. Augmentation regimens include the following:
   a. Lithium: Adding lithium appears to help in treatment-resistant depression. The dosing is controversial, ranging from full doses to concentrations used for bipolar disorder to small doses.
   b. Thyroid: Adding thyroid is also effective for treatment-resistant depression. The effect is not dependent on thyroid dysfunction. T₃ appears more effective than T₄. The usual dose is 25 mcg/day.
   c. Buspirone has also been used as an augmenting agent.
   d. Second-generation antipsychotics (SGAs or atypical antipsychotics) are also being used as adjuncts to antidepressant therapy. Almost all of them have been used, but only aripiprazole and Seroquel XR have received FDA approval for this indication. Olanzapine in combination with fluoxetine is also approved for treatment-resistant depression.

O. Treatment Algorithms

2. The STAR*D study is a large trial sponsored by the National Institute of Mental Health, designed to evaluate the effectiveness of a sequenced approach to therapy. A series of papers were published in 2006 in the *American Journal of Psychiatry* and *The New England Journal of Medicine* describing some of the results. Highlights include the following:

- a. All patients were initially treated with citalopram monotherapy, and only about 30% achieved remission.
- b. Patients who did not achieve remission were then allowed to select a “switch” strategy or “augmentation” strategy (level 2). Options included bupropion, sertraline, venlafaxine, or cognitive therapy. There were no significant differences between strategies, but slightly higher remission rates occurred with augmentation. Bupropion and buspirone augmentation worked similarly, and the former agent was better tolerated.
- c. Patients not responding to level 2 were then allowed to change to mirtazapine or nortriptyline or to have augmentation with lithium or thyroid. Again, there were not many differences. Thyroid augmentation worked as well as lithium.
- d. Remission rates decreased at each level of treatment. Although data from this trial will continue to be analyzed, the results suggest that less than one-third of patients achieve remission with initial SSRI monotherapy, and switching or augmentation strategies are viable options, with no marked increase in efficacy with either strategy. Switching antidepressants may be a good option for patients who do not respond to or do not tolerate a drug, and augmentation may be good for partial responders. However, continued monitoring of these observations is necessary to confirm these results.
- e. For a good review of the STAR*D findings, see Rush A et al. *Am J Psychiatry* 2006;163:1905-17.

### Patient Cases

*Questions 5–7 pertain to the following case:*

J.L. is a 26-year-old man with a history of type I bipolar disorder who presents to the inpatient unit with delusions that the Federal Bureau of Investigation is tracking his movements and that his thoughts are being recorded in a secret government database. He believes he has special powers to hide by making himself invisible. He is hyper-verbal and has not slept in the past 48 hours. He is placed on a 72-hour hold for control of his manic symptoms. He has a history of nonadherence to medications and is currently not taking any medications. J.L.’s last hospitalization was 2 months ago, when he had significant depressive symptoms and suicidal ideation. He has three or four hospitalizations per year, and his history of medication trials includes carbamazepine, olanzapine, and lamotrigine (may be helpful but uncertain because of nonadherence). He has also received a diagnosis of hepatitis C.

5. Which statement is most applicable for selecting J.L.’s mood stabilizer at this time?
   - A. Carbamazepine should be tried again because it is effective for preventing rehospitalization.
   - B. Divalproex should be tried because it is good for maintenance treatment.
   - C. Lithium should be tried because it can effectively treat the manic phase and prevent future episodes.
   - D. Lamotrigine should be tried again because it is effective for bipolar maintenance.

6. Which adverse effects would be of most concern and would require immediate evaluation if J.L. were prescribed lithium?
   - A. Hyperthyroidism.
   - B. Coarse tremor.
   - C. Severe acne.
   - D. Weight gain.
Patient Cases (continued)

7. It is 3 months later, and J.L. has been stable on lithium 900 mg/day. During a clinic visit, you find that J.L. is confused and slurring his words. His other medications include lisinopril, ibuprofen, atorvastatin, and zolpidem. Which is best to recommend immediately?
   A. Discontinue lisinopril because it interacts with lithium.
   B. Discontinue zolpidem because it may increase confusion.
   C. Obtain a lithium level because J.L. may have supratherapeutic levels.
   D. Discontinue ibuprofen because it interacts with lithium.

II. BIPOLAR DISORDER

A. Overview of Bipolar Disorder
   1. The DSM-5 defines bipolar disorder by the experience of a manic or hypomanic episode. Mania can be thought of as the affective opposite of depression. Consult the DSM-5 for a complete description of the diagnostic criteria. A manic episode is characterized by at least 1 week of an abnormal and persistently elevated mood accompanied by an increased amount of activity. Other symptoms include inflated self-esteem, irritability, decreased need for sleep, pressured speech, flight of ideas, poor attention, increased hyperactivity or agitation, and involvement in high-risk, pleasurable activities without respect to the consequences. A hypomanic episode is a milder form mania. It must exist for 4 days or longer. Unlike mania, it is not severe enough to warrant hospitalization, does not impair social or occupational functioning, and is not associated with psychosis.
   2. The DSM-5 includes two types of bipolar disorder:
      a. Bipolar I (BP I): Chronic disorder marked by one or more manic or mixed episodes and major depressive episodes
      b. Bipolar II (BP II): Chronic disorder marked by one or more major depressive episodes, accompanied by at least one hypomanic episode
      c. Cyclothymic disorder: Several periods of hypomania and mild depression, none of which meet the criteria for mania or major depressive episode
      d. Rapid cycling: At least 4 episodes of mania or depression in 1 year
   3. Bipolar disorder, particularly type II bipolar disorder, is often misdiagnosed as major depression. The diagnosis is important because the two conditions are treated differently.

B. Lithium for Bipolar Disorders
   1. The exact mechanism of action for lithium is unknown, but it appears to be neuroprotective.
   2. Lithium continues to be the gold standard for treating bipolar disorder type I. It is effective for the manic and depressive components. Although it is not a particularly good antidepressant as monotherapy in unipolar depression, it is effective in patients with bipolar disorder.
   3. Antimanic effects can occur in 1–2 weeks. Most clinicians use antipsychotics or benzodiazepines as adjunctive therapy during this period to cover the agitation and other symptoms. Antidepressant effects may take 6–8 weeks.
   4. Pharmacokinetics: Its half-life is 20–24 hours. It is excreted 95% unchanged by glomerular filtration, and anything that alters glomerular filtration rate affects its clearance. Pharmacokinetic methods are available for early prediction of doses, but waiting 5–6 days for steady state seems to work just as well.
   5. Initial dosing is in the range of 600–900 mg/day in divided doses and then titrated according to response and tolerability. Maintenance doses are based on serum concentrations, symptom relief, and the occurrence of adverse effects.
6. A pre-lithium workup includes a complete blood cell count, electrolytes, renal function, thyroid function tests, urinalysis, electrocardiogram (ECG), and pregnancy test for women of childbearing age.

7. Monitoring: Serum concentrations must be monitored. The half-life is about 1 day, so steady state occurs in about 5 days. Even if it is not steady state, it may be prudent to obtain a serum concentration 3 days after dosage changes. Most clinicians will aim for concentrations of 0.8–1.2 mEq/L in acute mania and 0.6–1.0 mEq/L during maintenance. Concentration-response data are based on 12-hour post-dose concentrations, so order levels in the morning 12 hours after the last evening dose. Perform renal function tests, thyroid function tests, and a urinalysis every 6–12 months.

8. Adverse effects are common with lithium and are most common during therapy initiation or after dose changes. Some points to consider are listed in Table 4.

9. Symptoms of lithium toxicity include lethargy, coarse tremor, confusion, seizures, and coma and may even result in death. Patients who present to urgent care on lithium therapy should always be monitored for lithium toxicity before any medication adjustments are made. Lithium level and sodium/renal function should be drawn so that lithium levels can be accurately estimated.

### Table 4. Adverse Effects Associated With Lithium

<table>
<thead>
<tr>
<th>Problem</th>
<th>Potential Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash or ↑ psoriasis</td>
<td>Discontinue the drug temporarily or permanently</td>
</tr>
<tr>
<td>Tremor</td>
<td>Reduce dose (Cp); add β-blocker</td>
</tr>
<tr>
<td>CNS toxicity (e.g., agitation, confusion)</td>
<td>Reduce dose (Cp)</td>
</tr>
<tr>
<td>Gastrointestinal (nausea, vomiting, diarrhea)</td>
<td>Reduce dose; try extended-release product</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Discontinue Li or give levothyroxine</td>
</tr>
<tr>
<td>Polydipsia or polyuria</td>
<td>Reduce dose, manage intake, and try amiloride or HCTZ, but know that HCTZ will ↑ Li Cp; single bedtime dosing helps</td>
</tr>
<tr>
<td>Interstitial fibrosis, glomerulosclerosis</td>
<td>Controversial! Keep dose at lowest effective concentration</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Avoid during first trimester, if possible</td>
</tr>
</tbody>
</table>

CNS = central nervous system; Cp = plasma concentration; HCTZ = hydrochlorothiazide; Li = lithium.
10. Situations to consider during lithium therapy are listed in Table 5.

**Table 5. Situations to Consider During Lithium Therapy**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Factors</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug interactions</td>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td>Thiazides</td>
<td>↑ Li Cp; avoid use to reduce toxicity</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>Little effect</td>
<td></td>
</tr>
<tr>
<td>Amiloride</td>
<td>Little effect</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>↑ Li Cp; avoid use to reduce toxicity</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>↓ Li Cp</td>
<td></td>
</tr>
<tr>
<td>ACEIs</td>
<td>↑ Li Cp; avoid use to reduce toxicity</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular blockers</td>
<td>Li prolongs action</td>
<td></td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Li may potentiate EPS</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↑ CNS toxicity</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>Li ↓ synthesis and release of thyroid hormone</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>↑ GFR</td>
<td>↓ Li Cp</td>
</tr>
<tr>
<td>Aging</td>
<td>↓ GFR</td>
<td>↓ Li requirements</td>
</tr>
<tr>
<td>↓ Renal function</td>
<td>↑ Sensitivity to ADRs</td>
<td>Li toxicity</td>
</tr>
<tr>
<td>Dehydration, salt restriction, and extrarenal salt loss</td>
<td>↑ Sodium reabsorption</td>
<td>↑ Li Cp</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitor; ADRs = adverse drug reactions; BUN = blood urea nitrogen; CNS = central nervous system; Cp = concentration of drug plasma; EPS = extrapyramidal symptoms; GFR = glomerular filtration rate; Li = lithium; NSAIDs = nonsteroidal anti-inflammatory drugs.

C. Anticonvulsants for Bipolar Disorder: These are also considered mood-stabilizing drugs that reduce manic and depressive episodes. Refer to the Neurology chapter for additional drug-specific details.

1. Divalproex: It is as effective as lithium in acute and prophylactic management. It appears to be good for rapid cyclers but may not be as effective during depressive episodes. It is also beneficial for patients with dysphoric mania, mixed episodes, or a history of substance abuse. Target serum concentrations range from 50 to 125 mcg/mL. The serum concentration can be checked 3–5 days after initiation or after a change of dose. Hypoalbuminemia increases the risk of increased free concentrations. Nonresponse to treatment is common if the dose is too low; however, the free fraction increases as the serum concentration is increased (above 100–125 mcg/mL). Dose-related adverse effects that occur at serum concentrations greater than 80 mcg/mL include neurotoxicity, sedation, hair loss, and thrombocytopenia. Life-threatening pancreatitis can occur but rarely (less than 5%). It can recur with reinitiation of valproate. The extended-release product has lower bioavailability than the enteric-coated preparation. The dose should be increased by 8%–20% when converting to the extended-release product.

2. Carbamazepine: This drug also appears effective for acute mania and maintenance therapy, particularly in patients with an history of head injury. Equetro is approved by the FDA for acute manic and mixed episodes. Although the same serum concentration range as for seizures (4–12 mcg/mL) should be used, keep in mind that clinicians may push it higher on the basis of tolerability and effect. Carbamazepine can also be added to lithium for patients who have not responded to monotherapy.
3. Lamotrigine: This drug has been approved for maintenance therapy. It appears particularly effective against the depressed phase of bipolar disorder. It is less effective than other mood stabilizers in the manic phase.
   a. A Stevens-Johnson type rash occurs in about 0.3% of adults and 1% of children. Lamotrigine must be discontinued if a rash occurs and should never be rechallenged. Risk increases with rapid dose titrations, high doses, young age, and concurrent use of valproic acid. The rash most commonly occurs within the first 2–8 weeks of therapy.
   b. The dose titration must be halved if lamotrigine is given with valproate and doubled if given with carbamazepine because of increased lamotrigine metabolism. The titration period is lengthy, so the onset of therapeutic effect can be delayed. For this reason, lamotrigine is not helpful in the acute setting.
   c. Lamotrigine has been associated with aseptic meningitis in adult and pediatric patients. Patients who experience headache, fever, chills, nausea, vomiting, stiff neck, rash, abnormal sensitivity to light, drowsiness, or confusion while taking lamotrigine should contact their health care professional right away. In 15 of 40 identified cases of aseptic meningitis, symptoms returned when patients were rechallenged with lamotrigine. Symptoms have occurred 1–42 days after the drug is started, and many of the patients required hospitalization.
4. Topiramate is also being used for bipolar disorder, but comparative data with other anticonvulsants are unavailable. It should be used with caution, however, because it has been linked with depression. Other anticonvulsants, including levetiracetam and oxcarbazepine, are being used for bipolar disorder, but data about efficacy are scarce. Data for gabapentin suggest it is ineffective.

D. Antipsychotics for Bipolar Disorder: Antipsychotics, particularly atypicals or second generation, have mood stabilizing properties. They can be used alone or with anticonvulsant mood stabilizers to treat bipolar symptoms. Metabolic adverse effects associated with antipsychotic use should be considered when medications are administered long term (see Schizophrenia section).
   1. Acute treatment: Antipsychotics treat acute symptoms of mania, including psychosis, aggression, or irritation. They are often combined with a traditional mood stabilizer for severe symptoms. All atypical antipsychotics have received FDA approval for use in acute mania or mixed episodes except for clozapine and iloperidone. For acute mania, the Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders (CANMAT/ISBD) guidelines include olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, asenapine, and paliperidone extended release among first-line agents.
   2. Bipolar depression: Both quetiapine and lurasidone are approved for treatment of bipolar depression. Data for aripiprazole suggest it is suboptimal for the treatment of bipolar depression.
   3. Maintenance treatment: Risperdal Consta and Abilify Maintena have been approved for use in bipolar maintenance as monotherapy. The CANMAT/ISBD guidelines additionally recommend olanzapine and quetiapine.

E. Benzodiazepines for Bipolar Disorder: These agents are acutely helpful for agitation but are not as helpful for the core symptoms, nor do they prevent relapses. They are particularly useful for insomnia, hyperactivity, and agitation. Lorazepam or diazepam is often used in the acute setting, but long-term therapy is not recommended.
F. Antidepressants for Bipolar Disorder:
   1. Use of these agents in bipolar disorder is controversial. There is a potential for switching to the manic phase, particularly in patients with type I bipolar disorder. The risk appears greater with TCAs and SNRIs than with SSRIs or bupropion. Because individual patients with bipolar disorder might benefit from antidepressants, the ISBD stopped short of recommending against any use of antidepressants. Antidepressants should not be used as monotherapy, and their use should be minimized in general. Antidepressants should not be used in bipolar depression if symptoms of mania are also present. The Systematic Treatment Enhanced Program for Bipolar Disorder trials found no statistically significant increased episodes of depression in patients taking mood stabilizers who discontinued their antidepressants. Patients with bipolar disorder taking mood stabilizers who received either paroxetine or bupropion were no more likely to achieve remission or have a durable recovery than those receiving placebo. They were also no more likely to experience a switch to a manic phase (Sachs GS, et al. N Engl J Med 2007;356:1711-22).
   2. Fluoxetine in combination with olanzapine is approved to treat depression associated with bipolar disorder type I.

G. Bipolar type II: The depressive phase tends to be more debilitating. Patients are usually functional during hypomanic episodes. Quetiapine is the agent of choice for depression. Lamotrigine is a reasonable alternative. Other mood stabilizers can be used but may not be as efficacious as for type I. Antidepressants are used more frequently but should never be used alone.

Patient Cases

Questions 8–11 pertain to the following case:
L.M. is a 25-year-old man recently given a diagnosis of schizophrenia, paranoid type. He often hears voices telling him that he is "stupid and worthless" and that he should "just jump off his apartment building." His parents became very concerned about his isolative behavior and brought him to the hospital. He was given haloperidol in the psychiatry unit and now presents with neck stiffness and feelings of extreme restlessness. Until now, he has not taken medications because he felt that he could control his symptoms on his own with vitamins and Red Bull drinks.

8. Which is the most appropriate treatment of L.M.'s symptoms at this time?
   A. Benztropine.
   B. Haloperidol.
   C. Olanzapine.
   D. Quetiapine.

9. You and the psychiatric team decide to recommend risperidone for L.M. Which is the most likely reason for this selection?
   A. Risperidone has less risk of causing EPS than haloperidol.
   B. Risperidone is available in a long-acting injection to increase adherence.
   C. Risperidone is effective for decreasing L.M.'s negative symptoms.
   D. Risperidone can be dosed once daily after titration to target dose.
**Patient Cases (continued)**

10. Which is the best example of an adverse effect of risperidone that would be of concern in L.M.?
   A. Sedation.
   B. Anticholinergic effects.
   C. EPS.
   D. Corrected QT (QTc) prolongation.

11. One year later, L.M. is no longer responding to risperidone, and you decide to switch him to another medication. L.M. is interested only in oral medications. Given his history, which agent is most appropriate at this time?
   A. Clozapine.
   B. Fluphenazine.
   C. Olanzapine.
   D. Quetiapine.

**III. SCHIZOPHRENIA**

A. Characteristics

1. Schizophrenia is a thought disorder characterized by a mix of symptoms. Five symptoms are involved in the diagnosis, and at least 2 of them must be present for at least 1 month. At least one of the three must be hallucinations, delusions, or disorganized speech. Patients may also have disorganized or catatonic behavior or negative symptoms.

2. Several symptom domains have been developed for schizophrenia. Usually, symptoms are divided into two categories: positive and negative. However, other domains have also been suggested. The most common scheme is shown in Table 6.

<table>
<thead>
<tr>
<th>Table 6. Categories of Schizophrenia-Associated Symptoms</th>
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</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
</tr>
<tr>
<td>(presence of something that should not be there)</td>
</tr>
<tr>
<td>Traditional and Atypical Antipsychotics Effective</td>
</tr>
<tr>
<td>Hallucinations&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Delusions&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paranoia or suspiciousness&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Conceptual disorganization&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hostility&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Grandiosity&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Excitement&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
</tr>
<tr>
<td>(absence of something that should be present)</td>
</tr>
<tr>
<td>Atypical Antipsychotics May or May Not Be More Effective</td>
</tr>
<tr>
<td>Blunted or flat affect&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Social withdrawal (passive-apathetic)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lack of personal hygiene&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prolonged time to respond&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Poor rapport&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Poor abstract thinking&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Poverty of speech (lack of spontaneity and flow of conversation)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Cognitive</strong></td>
</tr>
<tr>
<td>No Current Medications Effectively Treat This</td>
</tr>
<tr>
<td>Poor executive function</td>
</tr>
<tr>
<td>Impaired attention</td>
</tr>
<tr>
<td>Impaired working memory (does not learn from mistakes)</td>
</tr>
</tbody>
</table>
Table 6. Categories of Schizophrenia-Associated Symptoms (continued)

<table>
<thead>
<tr>
<th>Positive</th>
<th>Negative</th>
<th>Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>(presence of something that should not be there)</td>
<td>(absence of something that should be present)</td>
<td></td>
</tr>
<tr>
<td>Loose associations</td>
<td>Emotional withdrawal(^b)</td>
<td></td>
</tr>
<tr>
<td>Thought broadcasting</td>
<td>Alogia (inability to carry on logical conversation)</td>
<td></td>
</tr>
<tr>
<td>Thought insertion</td>
<td>Ambivalence (simultaneous, contradictory thinking); prevents decision-making</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autism (internally directed)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amotivation (avolition)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anhedonia</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)These symptoms can be used as a brief clinical assessment for antipsychotic response; they are known as the 4-Item Positive Symptoms Rating Scale (PSRS) and the Brief Negative Symptom Assessment (BNSA).

\(^b\)These symptoms are used to score the positive and negative portions of the Positive and Negative Symptom Scale (PANSS).

\(^c\)Conceptual disorganization, according to the Brief Psychiatric Rating Scale, is the “degree to which speech is confused, disconnected, vague or disorganized.” This includes tangential thinking, circumstance, sudden topic shifts, incoherence, derailment, blocking, neologisms, clangs, word salad, and other speech disorders.

3. Terms associated with schizophrenia
   a. Delusions: These are erroneous beliefs involving misinterpretations of reality that are resistant to evidence refuting them. A fixed delusion will not change, no matter how much evidence is offered to the contrary.
   b. Hallucinations: These perceptual abnormalities can involve any sensory system. With schizophrenia, auditory hallucinations are most common. These can be persecutory (e.g., someone is going to get me), paranoid (e.g., someone is watching), or command (e.g., someone told me to do it).
   c. Thought disorder: This is manifested in several ways. “Loose associations” refers to the person going from one topic to another as though the topics were connected. “Tangential” speech refers to answers to questions that are only slightly related or totally unrelated to the question. “Word salad” refers to speech that is almost incomprehensible and is very much like receptive aphasia.

B. Course of Illness
   1. Onset is usually between adolescence and early adulthood. It occurs earlier in men (i.e., early 20s) than in women (i.e., late 20s to early 30s). The incidence is about equal between sexes.
   2. Most patients fluctuate between acute episodes and remission. Periods between episodes may include some residual symptoms.
   3. There are four phases of schizophrenia: prodromal, acute, stabilization, and stable.
      a. Prodromal phase: This phase is characterized by the gradual development of symptoms that may go unnoticed until a major symptom occurs. It may include isolation, deterioration of hygiene, loss of interest in work or school, and dysphoria.
      b. Acute phase: This is the full-blown episode of psychotic behavior. Patients may be unable to care for themselves during this phase.
      c. Stabilization phase: The acute symptoms begin to decrease, and this phase may last for several months.
      d. Stable phase: During this phase, symptoms have markedly declined and may not be present. Nonpsychotic symptoms such as anxiety and depression may be present.
   4. Complete remissions without symptoms are uncommon.
C. Causes
1. The causes of schizophrenia are unknown. It appears to involve neurophysiological and psychological abnormalities.
2. The primary neurotransmitters believed to be involved in the etiology are dopamine and serotonin. The exact relationship between these neurotransmitters remains unknown. It does appear that in some areas of the brain, dopamine overactivity results in some symptoms, whereas in others, underactivity may occur. Positron emission tomographic scanning shows areas of hypermetabolism and hypometabolism.
3. Many potential risk factors for schizophrenia have been identified, including having a family history of schizophrenia, having a poor birth history, experiencing intrauterine trauma, living in an urban area, having stress, and being born during the winter.

D. Rating Scales
1. The Brief Psychiatric Rating Scale (BPRS) is a general psychiatric rating scale that has been used to measure outcomes in clinical trials, including those involving schizophrenia.
2. The Positive and Negative Symptom Scale (PANSS) is a 30-item, 7-point scale that was partly adapted from the BPRS. It is widely used to evaluate antipsychotic therapy in clinical trials but not in daily clinical practice. It requires a 45-minute interview with the patient. The interviewer must be specially trained to administer it.
3. The Positive Symptoms Rating Scale (PSRS) and the Brief Negative Symptom Assessment (BNSA) are two different but complementary scales. Each consists of four items. Each of the items on the PSRS is scored from 1 (not present) to 7 (extremely severe). Each of the items on the BNSA is scored from 1 (normal) to 6 (severe). These scales were used in the Texas Algorithm Project, a large-scale clinical trial that assessed the value of algorithm-driven medication practices in the mentally ill. The PSRS and BNSA allow rapid clinical assessment.

E. First-Generation Antipsychotics (FGAs; also called typical or conventional antipsychotics) for Schizophrenia (Table 7)
1. This class of agents includes all the older antipsychotic agents. Chlorpromazine was the first agent used clinically.
2. These agents can be categorized according to chemical class or potency.

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Degree of EPS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation phenothiazines (typical or conventional)</td>
<td>Fluphenazine</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Trifluoperazine</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Perphenazine</td>
<td>+2/+3</td>
</tr>
<tr>
<td></td>
<td>Mesoridazine</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Thioridazine</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Chlorpromazine</td>
<td>+2</td>
</tr>
<tr>
<td>Butyrophenone</td>
<td>Haloperidol</td>
<td>+3</td>
</tr>
<tr>
<td>Others</td>
<td>Thiothixene</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Loxapine</td>
<td>+2/+3</td>
</tr>
</tbody>
</table>
Table 7. Antipsychotic Agents for the Treatment of Schizophrenia by Chemical Class (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Degree of EPS$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation antipsychotics (atypical)</td>
<td>Clozapine</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Paliperidone</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Iloperidone</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Asenapine</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Lurasidone</td>
<td>0/+1</td>
</tr>
</tbody>
</table>

$^a$0 = none; +1 = low; +2 = moderate; +3 = high.

EPS = extrapyramidal symptoms.

3. These drugs can also be categorized by potency as antagonists at dopamine D$_2$ receptors. They also possess anticholinergic, antihistaminic, and α-adrenergic blocking properties and tend to be worse with low-potency agents. The high-potency agents at dopamine D$_2$ have less potency at the other receptors; thus, the adverse effect profiles also differ by potency (Table 8).

Table 8. Select FGAs for the Treatment of Schizophrenia by Potency

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Equivalent (mg)</th>
<th>Potency$^a$</th>
<th>Anticholinergic$^b$</th>
<th>Sedation$^b$</th>
<th>↓ BP$^b$</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>100</td>
<td>Low</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>Low</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>100</td>
<td>Low</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>Low</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>10</td>
<td>Int.</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Int.</td>
</tr>
<tr>
<td>Loxapine</td>
<td>10–15</td>
<td>Int.</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>Int.</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>2</td>
<td>High</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>3–5</td>
<td>High</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>High</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2–3</td>
<td>High</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>High</td>
</tr>
</tbody>
</table>

$^a$Potency = D$_2$ receptor affinity
$^b$Scale 1–5 = low to high.
BP = blood pressure; EPS = extrapyramidal symptoms; FGA = first-generation antipsychotic; Int. = intermediate.

4. Sedation: The degree of sedation depends on the drug. If sedation occurs, it is usually worse initially and is then tolerated better with time. It tends to be dose-related.

5. Anticholinergic effects: Dry mouth, constipation, blurred vision, and urinary hesitancy can occur. Patients for whom these effects may be a problem should probably receive a high-potency agent.

6. Antiadrenergic effects: The α-adrenergic blocking effect is seen as orthostatic hypotension. Patients who are predisposed to such effects (e.g., older adults, dehydrated patients) should probably receive a high-potency agent.

7. Extrapyramidal symptoms
   a. Parkinsonism: This is manifested by symptoms such as bradykinesia, rigidity, tremor, or akinesia. It is usually responsive to anticholinergic agents such as diphenhydramine, trihexyphenidyl, and benztropine.
b. Dystonia: Examples include torticollis, laryngospasm, and oculogyric crisis. This is also treated with anticholinergics.

c. Akathisia: This is a somatic restlessness and inability to stay still or calm. Reducing the antipsychotic dose and switching to an agent with a lower incidence of akathisia are the best options but not always feasible. It responds poorly to anticholinergics. Lipophilic (fat soluble) β-blockers such as propranolol and nadolol are effective and are the agents of choice.

d. Tardive dyskinesia: Characterized by abnormal involuntary movements that occur with long-term antipsychotic therapy. It usually involves the orofacial muscles and is often insidious. If caught early, it can be reversible. With continued drug exposure, particularly at high doses, it is often irreversible. Risks are probably related to total cumulative dose. Symptoms may decrease with lowering the dose of antipsychotic or switching to an agent that is associated with less tardive dyskinesia. This dose reduction must be weighed against worsening of schizophrenic symptoms. The risk is higher with FGAs than SGAs, as well as older age. Clozapine has not been associated with tardive dyskinesia, and changing to this drug is preferred in patients with moderate to severe symptoms. The other atypical antipsychotics also appear to have a low potential to cause tardive dyskinesia. Anticholinergic agents should not be given to treat tardive dyskinesia and may actually worsen the symptoms.

8. Neuroleptic malignant syndrome: This is another serious complication. It occurs with all agents but appears more common with high-potency drugs. It is manifested by agitation, confusion, changing levels of consciousness, fever, tachycardia, labile blood pressure, and sweating. Its mortality rate is high, and it should be taken seriously. Discontinue the offending agent and give supportive therapy, including fluids and cooling. Bromocriptine and dantrolene have been used with varying success.

9. Endocrine effects: Galactorrhea and menstrual changes can occur because of hyperprolactinemia caused by antipsychotics. Prolactin secretion is blocked by dopamine. Dopamine blockers can increase prolactin concentrations (hyperprolactinemia).

10. Weight gain: This occurs in up to 40% of patients, with low-potency agents having higher risk. Important interventions include keeping the dose as low as possible and implementing dietary management. Weight gain may occur because of actions at histamine or serotonin receptors.

11. Sexual dysfunction: Erectile problems occur in 23%–54% of men. Loss of libido and anorgasmia may occur in men and women.

12. Venous thromboembolism (VTE): A published nested case-control study of older adults from the United Kingdom showed that FGAs and SGAs were associated with greater risk of deep VTE or pulmonary embolism than matched controls (Parker C et al. BMJ 2010;341:c4245). Patients from primary care with schizophrenia, bipolar disorder, or dementia who had been prescribed antipsychotics in the past 24 months had a 32% elevated risk of VTE (odds ratio = 1.32 [95% confidence interval, 1.23–1.42]) and a 56% elevated risk if the treatment had been in the past 3 months. Second-generation antipsychotics had a higher risk of VTE than did first-generation drugs (73% vs. 28%, respectively). The study was limited by possible confounders such as smoking status and body mass index, although these factors were deemed not to have considerably altered the results.

13. Miscellaneous: Low-potency agents such as thioridazine and chlorpromazine can cause pigmented deposits on the retina and corneal opacity. Many of the typical agents can cause serious changes on the ECG (e.g., prolongation of the QTc interval). These changes can lead to arrhythmias and death.

14. Therapy initiation: In the past, acute episodes were treated very aggressively with high doses, and the process was called neuroleptization. Because neuroleptization can lead to adverse effects and is probably no more effective than starting with full therapeutic doses, it is no longer advocated. Dosing during the stabilization phase may be less aggressive, but a very low dose increases the risk of relapse.
15. Administration route: Oral therapy is most common; however, parenteral drugs can be used acutely if the patient does not adhere to therapy or is agitated and will not take oral medications. Haloperidol can be given intramuscularly. Intravenous haloperidol has been linked to toxicity including torsades de pointes and should not be given. Depot forms of haloperidol and fluphenazine are available, providing sustained concentrations for about 1 month for haloperidol and 2–3 weeks for fluphenazine. These are indicated only for chronic therapy in patients who have trouble adhering to oral therapy. Fluphenazine decanoate requires “bridging” with oral therapy when treatment is begun.

16. Therapy duration: Continuation of therapy during the stable phase is of concern because of the risk of adverse effects (e.g., the tardive dyskinesia associated with the older agents). This is of less concern with the newer drugs. Relapse rates are more than 50% during the first year or so after discontinuing these agents for both first-episode patients and patients who relapse; thus, maintaining the antipsychotic at the minimal effective dose continuously may be the best approach for most patients. Some first-episode patients may be tried off drugs after being symptom free for 2 years. Those with a history of episodes should probably be symptom free for 5 years before discontinuation is considered. Long-term therapy should include monitoring for metabolic complications such as diabetes, weight gain, and lipid abnormalities.

F. Second-Generation Antipsychotics for Schizophrenia

1. SGAs (or atypical antipsychotics) were developed to reduce EPS adverse effects and tardive dyskinesia and to improve efficacy. The characteristics that define “atypicality” are not all agreed on, but in general, they all share at least three characteristics: The risk of EPS is lower than with typical antipsychotics at usual clinical doses, the risk of tardive dyskinesia is reduced, and the ability to block serotonin-2 receptors is present. This third property may improve activity for the negative symptoms of schizophrenia and reduce the risk of EPS. Many clinicians see atypical drugs as first-line agents, despite the higher acquisition costs of the brand name agents. Atypical agents (particularly clozapine and olanzapine) have been associated with new-onset diabetes mellitus and metabolic syndrome. All patients prescribed atypical antipsychotics should be monitored for weight, blood pressure, fasting glucose, lipids, and waist circumference at baseline and periodically thereafter.

2. Clozapine (Clozaril): Clozapine is a less potent dopamine blocker than typical antipsychotics and is a serotonin-2 antagonist. Some of its action may be attributable to D₁ antagonism. It is as effective as typical agents, is not associated with EPS or tardive dyskinesia, and may lead to an improvement in negative symptoms more effectively than typical drugs. It is also effective for many patients who have not responded to typical agents. It appears to affect brain regions selectively, particularly those that control the cognitive and affective states altered in people with schizophrenia (i.e., the mesolimbic A10 tract, but not the A9 tract, which modulates movement). Adverse effects have limited the use of this agent.

   a. Agranulocytosis: This is manifested as a reduction in white blood cell count, and it increases the risk of serious or fatal infections. It is contraindicated if the white blood cell count is less than 3500 cells/mm³ (Table 9). The incidence is about 1%–2% and is highest during the first 4–6 months of therapy. Because of this risk, patients must have a weekly complete blood cell count for 6 months and then every 2 weeks after that while taking the drug. The frequency can be decreased to monthly after 1 year if the white blood cell count is greater than 3500 cells/mm³ and the absolute neutrophil count is greater than 2000 cells/mm³. If the white blood cell count is significantly decreased during therapy (less than 3000 cells/mm³), the drug should be discontinued. Patients must be enrolled in a Clozaril registry program (Clozaril National Registry, Teva Clozapine National Registry), which monitors the reporting of absolute neutrophil and white blood cell counts.
<table>
<thead>
<tr>
<th>Situation</th>
<th>Hematologic Values for Monitoring</th>
<th>Frequency of WBC and ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation of therapy</td>
<td>WBC ≥3500 cells/mm³ and ANC ≥2000 cells/mm³ Note: Do not initiate in patients with (1) history of myeloproliferative disorder or (2) clozapine-induced agranulocytosis or granulocytopenia</td>
<td>Weekly for 6 months</td>
</tr>
<tr>
<td>6–12 months of therapy</td>
<td>All results for WBC ≥3500 cells/mm³ and ANC ≥2000 cells/mm³</td>
<td>Every 2 weeks for 6 months</td>
</tr>
<tr>
<td>12 months of therapy</td>
<td>All results for every WBC ≥3500 cells/mm³ and ANC ≥2000 cells/mm³</td>
<td>Every 4 weeks ad infinitum</td>
</tr>
<tr>
<td>Immature forms present</td>
<td>N/A</td>
<td>Repeat WBC and ANC</td>
</tr>
<tr>
<td>Therapy discontinuation</td>
<td>N/A</td>
<td>Weekly for at least 4 weeks from day of discontinuation or until WBC ≥ 3500 cells/mm³ and ANC &gt; 2000 cells/mm³</td>
</tr>
<tr>
<td>Substantial drop in WBC or ANC</td>
<td>Single drop or cumulative drop within 3 weeks of WBC ≥3000 cells/mm³ or ANC ≥1500 cells/mm³</td>
<td>1. Repeat WBC and ANC 2. If repeat values are 3000 cells/mm³ ≤ WBC ≥ 3500 cells/mm³ and ANC &lt; 2000 cells/mm³, then monitor twice weekly</td>
</tr>
<tr>
<td>Mild leukopenia, mild granulocytopenia</td>
<td>3500 cells/mm³ &gt; WBC ≥ 3000 cells/mm³ or 2000 cells/mm³ &gt; ANC ≥ 1500 cells/mm³</td>
<td>Twice weekly until WBC &gt; 3500 cells/mm³ and ANC &gt; 2000 cells/mm³, then return to previous monitoring frequency</td>
</tr>
<tr>
<td>Moderate leukopenia, moderate granulocytopenia</td>
<td>3000 cells/mm³ &gt; WBC ≥ 2000 cells/mm³ or 1500 cells/mm³ &gt; ANC ≥ 1000 cells/mm³</td>
<td>1. Interrupt therapy 2. Daily until WBC &gt; 3000 cells/mm³ and ANC &gt; 1500 cells/mm³ 3. Twice weekly until WBC &gt; 3500 cells/mm³ and ANC &gt; 2000 cells/mm³ 4. May rechallenge when WBC &gt; 3500 cells/mm³ and ANC &gt; 2000 cells/mm³ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum</td>
</tr>
<tr>
<td>Severe leukopenia, severe granulocytopenia</td>
<td>WBC &lt;2000 cells/mm³ or ANC &lt;1000 cells/mm³</td>
<td>1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC &gt; 3000 cells/mm³ and ANC &gt; 1500 cells/mm³ • Twice weekly until WBC &gt; 3500 cells/mm³ and ANC &gt; 2000 cells/mm³ • Weekly after WBC &gt; 3500 cells/mm³</td>
</tr>
</tbody>
</table>
Table 9. Hematologic Monitoring for Clozapine (continued)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Hematologic Values for Monitoring</th>
<th>Frequency of WBC and ANC Monitoring</th>
</tr>
</thead>
</table>
| Agranulocytosis    | ANC ≤500 cells/mm³                | 1. Discontinue treatment and do not rechallenge patient  
|                    |                                  | 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows:  
|                    |                                  | • Daily until WBC > 3000 cells/mm³ and ANC > 1500 cells/mm³  
|                    |                                  | • Twice weekly until WBC > 3500 cells/mm³ and ANC > 2000 cells/mm³  
|                    |                                  | • Weekly after WBC > 3500 cells/mm³  

ANC = absolute neutrophil count; WBC = white blood cell count.

b. Common adverse effects: These include weight gain, sedation, hypersalivation, rapid heart rate, orthostatic hypotension, and fever. Note that the presence of fever should alert the clinician to the possibility of infection and agranulocytosis. There are also black box warnings for seizures (more frequent at higher doses) and myocarditis, orthostatic hypotension, and respiratory arrest. If the drug is discontinued for 48 hours or more, retitration is required to avoid orthostatic hypotension.

3. Aripiprazole (Abilify): This drug’s pharmacology differs from that of other atypical agents. It is a dopamine D₂/serotonin-1 partial agonist and a serotonin-2 antagonist, sometimes called a dopamine-serotonin–stabilizing agent. It has a low risk of most forms of EPS, including tardive dyskinesia. It is associated with a high incidence of akathisia.

4. Asenapine (Saphris) is available in a sublingual formulation. It appears to have a lower risk of metabolic effects and EPS; however, it has been associated with a high risk of orthostasis and sedation. There has also been a warning about the risk of hypersensitivity reactions with asenapine.

5. Iloperidone (Fanapt) appears to have a lower risk of metabolic effects. It also has a higher risk of orthostasis but a lower risk of EPS, anticholinergic symptoms, and sedation. Short- and long-term studies have also shown an association with QTc prolongation similar to that of haloperidol and ziprasidone.

6. Lurasidone (Latuda) has a low risk of metabolic and cardiac effects together with a low EPS risk. It has potent antagonistic activity at serotonin-7 and a high affinity to serotonin-1A receptors, which is theorized to have beneficial cognitive and anxiolytic effects. The maximal daily dose has recently been increased to 160 mg/day, and it should be taken with food. The recommended starting dose for moderate and severe renal impairment and when used with a moderate CYP3A4 inhibitor (e.g., diltiazem) is 20 mg, and the maximal dose is 80 mg. The recommended starting dose for moderate and severe hepatic impairment is 20 mg, and the maximal dose is 80 mg in moderate hepatic impairment and 40 mg in severe hepatic impairment.

7. Olanzapine (Zyprexa): This drug is structurally similar to clozapine and has a similar pharmacology. Unlike clozapine, however, it has not been associated with agranulocytosis. Olanzapine may affect only the A10 tract of the mesolimbic system. In one study, negative symptoms responded better than with haloperidol. Along with clozapine, olanzapine carries the highest risk for diabetes. For this reason, the PORT guidelines do not consider it a first-line treatment.

8. Paliperidone (Invega) is an active metabolite of risperidone (see below). Paliperidone palmitate is also available as a monthly depot injection.

9. Quetiapine (Seroquel): Offers a low incidence of EPS. Quetiapine is also the preferred antipsychotic if psychosis occurs in a patient with Parkinson disease.
10. Risperidone (Risperdal): This drug is a potent dopamine D<sub>2</sub> antagonist and a serotonin-2 antagonist. It has limited anticholinergic activity. At doses of up to 6 mg/day, the incidence of EPS has been no higher than with placebo in clinical studies. However, EPS is a dose-related phenomenon that may occur in patients taking the drug even at usual doses. Patients often tolerate risperidone better than haloperidol. It probably has no advantage in patients requiring high doses of antipsychotics. Adverse effects include sedation, orthostatic hypotension, weight gain, sexual dysfunction, and hyperprolactinemia. A long-acting intramuscular formulation (risperidone [Risperdal Consta]) is available that is better tolerated than the other intramuscular depot forms of antipsychotics. It is administered every 2 weeks and requires a 3-week bridge therapy with oral risperidone. It is generally used only after the patient is known to tolerate oral therapy. Like with long-acting risperidone, tolerability with oral therapy should be established before starting it.

11. Ziprasidone (Geodon): Use caution if combining it with other drugs (e.g., TCAs or antiarrhythmics) that can also increase the QTc interval. It is also available in a parenteral formulation for acute agitation. The drug must be taken with food to increase absorption. Electrocardiographic changes occur with antipsychotics. QTc prolongation can predispose the patient to ventricular arrhythmias including torsades de points syndrome. The risk appears highest with thioridazine, clozapine, ziprasidone, and iloperidone, although the other agents may do this to a lesser extent. Patients must be assessed for predisposing factors such as preexisting ECG abnormalities, electrolyte disturbances, and concurrent therapy with other drugs that prolong the QTc interval.

Table 10 summarizes the adverse effects associated with SGAs.

<table>
<thead>
<tr>
<th>Drug (generic/brand)</th>
<th>Metabolic Syndrome</th>
<th>Cardiac (clinically significant)</th>
<th>Sedation</th>
<th>Misc. Clinically Significant Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast Facts</strong></td>
<td>Weight gain</td>
<td>DM</td>
<td>Dyslipidemia</td>
<td>OH: tolerance builds over 2-3 mos.</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Little to none</td>
<td>No</td>
<td>Little to none</td>
<td>None</td>
</tr>
<tr>
<td>Asenapine (Saphris)</td>
<td>Little to None</td>
<td>Little to None</td>
<td>Low to none</td>
<td>Possible QTc prolongation, OH</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>Highest</td>
<td>Yes</td>
<td>High</td>
<td>OH, prolonged QTc tachycardia</td>
</tr>
<tr>
<td>Iloperidone (Fanapt)</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>QTc prolongation, OH</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>Low</td>
<td>Low</td>
<td>Low to none</td>
<td>None</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Highest</td>
<td>Yes</td>
<td>High</td>
<td>None</td>
</tr>
</tbody>
</table>
Table 10. Adverse Effects of SGAs (continued)

<table>
<thead>
<tr>
<th>Drug (generic/brand)</th>
<th>Metabolic Syndrome</th>
<th>Cardiac (clinically significant)</th>
<th>Sedation</th>
<th>Misc. Clinically Significant Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight gain</td>
<td>DM</td>
<td>Dyslipidemia</td>
<td>Possible QTc prolongation</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>Low</td>
<td>Low</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>OH</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Less</td>
<td>OH</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>Little</td>
<td>No</td>
<td>Less</td>
<td>Prolonged QTc</td>
</tr>
</tbody>
</table>

* Compared with thioridazine (30 msec), a FGA which is not used often due to its potential to cause torsade des pointes.

Key: EPS= extrapyramidal symptoms. OH=orthostatic hypotension

G. Adjunctive Medications
1. Lithium: This agent may augment antipsychotic action.
2. Anticonvulsants (carbamazepine and valproic acid): These agents may augment antipsychotics, but their role in therapy remains undetermined. They may be useful in patients with agitated or violent behavior.
3. Benzodiazepines: These may be useful during the acute phase for agitation or anxiety, but they are less effective for treatment of psychotic symptoms. These drugs must also be used with caution in patients with schizophrenia because this population is at high risk of substance abuse.

H. Comparisons of FGAs and SGAs
1. Almost all treatment guidelines now suggest that SGAs are the preferred first-line agents to typical drugs because most clinicians believe they are better tolerated and pose less risk. However, studies have questioned this conclusion. In these trials, the older agents appeared to do as well in efficacy and tolerability; however, they were not conclusive. Some issues with the study design limit the findings. Some clinicians may wish to use typical agents. There is certainly pressure from a cost standpoint. The results of a study named the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study were published in the October 2006 issue of Archives of General Psychiatry (Jones PB, et al. Arch Gen Psychiatry 2006;63:1079-87). The findings of this study suggest that the differences in the effect of FGAs and SGAs are not as much as had been thought.
2. The Clinical Antipsychotic Trials of Intervention Effectiveness study (CATIE, sponsored by NIMH) compared several SGAs with the older agent perphenazine. Here are some of the findings:
   a. Discontinuation
      i. High in all groups: 74% of all patients discontinued before 18 months
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ii. Olanzapine = 64%
iii. Perphenazine = 75%
iv. Quetiapine = 82%
v. Risperidone = 74%
vi. Ziprasidone = 79%

b. Time to discontinuation
i. All causes: Longest for olanzapine (significantly longer than for quetiapine and risperidone, not the others)
ii. Lack of efficacy: Longest for olanzapine (significantly longer than perphenazine, quetiapine, and risperidone, but not ziprasidone)

c. Duration of successful treatment: Longest for olanzapine (significantly longer than for quetiapine, risperidone, and perphenazine, as well as for risperidone compared with quetiapine)

d. Efficacy: Positive and Negative Syndrome Scale (PANSS) scores
i. Scores improved in all groups as time progressed.
ii. Initially, more improvement with olanzapine, but improvement diminished with time

e. Adverse drug reactions
i. Olanzapine: More often associated with weight gain and metabolic adverse effects
ii. Perphenazine: More often associated with EPS

3. Two meta-analyses of comparison trials were conducted. The first analysis of FGAs and SGAs suggested that clozapine, risperidone, and olanzapine were more effective than the FGAs evaluated. Other SGAs were not superior to FGAs. Further research is needed to resolve this issue (Leucht S, et al. Lancet 2009;373:31-41). In the second meta-analysis, SGAs were compared for the change in total PANSS score (Leucht S, et al. Am J Psychiatry 2009;166:152-63). Olanzapine was significantly more efficacious than aripiprazole (p=0.002), quetiapine (p<0.001), risperidone (p=0.006), and ziprasidone (p<0.001). Most of the efficacy differences were caused by improvement in positive, not negative, symptoms.

Patient Cases

*Questions 12–15 pertain to the following case:*

C.P. is a recent Iraq war veteran who has been treated successfully with paroxetine for his major depression for the past 3 weeks. He presents to the clinic experiencing nightmares, “feeling on edge all the time,” and having flashbacks of his time in the war. He is evaluated and given a diagnosis of posttraumatic stress disorder (PTSD). He has no history of substance dependence and has no significant medical history.

12. Which recommendation is most appropriate at this time?
   A. Continue paroxetine because it treats both PTSD and major depression.
   B. Discontinue paroxetine and initiate sertraline, which treats both PTSD and major depression.
   C. Continue paroxetine and add lorazepam for the anxiety symptoms.
   D. Discontinue paroxetine and initiate buspirone for the anxiety symptoms.

13. C.P. has been adherent to the medication you recommended earlier, but he still feels very irritable and has been aggressive at times at work toward others. Which adjunctive medication is most appropriate in this patient?
   A. Buspirone.
   B. Clonazepam.
   C. Divalproex.
   D. Lithium.
Patient Cases (continued)

14. After 8 months of treatment, C.P. is not responding to the medication you recommended. Having heard a lot about buspirone, he wonders whether this medication might be helpful for his conditions. Which is the most accurate statement for this patient?
   A. Buspirone may be helpful for the nightmares.
   B. Buspirone may work as quickly as 3 days.
   C. Buspirone is convenient because of its once-daily dosing.
   D. Buspirone does not have much dependence potential.

15. C.P. returns to the clinic and states that his depressive and anxiety symptoms are much improved. However, he is concerned that his girlfriend, who has OCD, is not doing well on her treatment with lorazepam. If you were also treating the girlfriend, which is the most appropriate medication you would initiate?
   A. Clomipramine.
   B. Amitriptyline.
   C. Imipramine.
   D. Nortriptyline.

IV. ANXIETY DISORDERS

A. Overview of Anxiety Disorders
   1. Generalized anxiety disorder (GAD) is characterized by 6 months or more of excessive worry or anxiety, generally with an unidentified cause.
   2. Panic disorder is characterized by discrete periods of sudden, intense fear or terror and feelings of impending doom. Usually, the precipitating cause is unknown, but the patient can become conditioned to believe it is attributable to some environmental cause.
   3. Agoraphobia: Intense fear in 2 or more settings (mostly in the open or in public). These settings include: using public transportation, being in open spaces, being in enclosed spaces, standing in line or being in a crowd, and being outside the home alone.
   4. OCD is characterized by obsessive or intrusive thoughts that cannot be controlled and that are repetitive. Compulsions are ritualistic behaviors (e.g., washing the hands, combing the hair, cleaning the house).
   5. PTSD follows a traumatic event. It is characterized by increased arousal and avoidance of stimuli that approximate the original traumatic event.
   6. Social anxiety disorder is characterized by marked and persistent fear and anxiety in social or performance situations that are recognized as excessive or unreasonable. These situations are either avoided or endured with intense anxiety.
   7. Specific phobias are characterized by intense fear or anxiety induced by a specific object.

B. Pharmacotherapeutic Options for Anxiety Disorders
   1. Benzodiazepines: These drugs have anxiolytic properties, and some have preventive efficacy for panic attacks. Depending on the choice of agent, the onset can be very rapid, as outlined below. The high-potency, short half-life agents are the most rapidly acting. They are effective for treating the acute somatic and autonomic symptoms of anxiety, but do not adequately address the underlying cognitive and psychologically pathology.
a. Pharmacologically, they share, to various degrees, five properties: (1) anxiolytic, (2) hypnotic, (3) muscle relaxation, (4) anticonvulsant, and (5) amnesic actions. Tolerance of the anxiolytic action is uncommon. Benzodiazepines are differentiated by their half-life (plus or minus active metabolites) and potency. If they are thought of as short half-life/high-potency versus long half-life/lower-potency drugs, the following distinctions can be made:

i. Short half-life/high potency: These are usually more rapid-acting agents that provide quicker control of the symptoms. However, tolerance of the hypnotic effect develops rapidly, withdrawal problems are common, and interdose breakthrough symptoms can occur. These are often used for acute management and later replaced with longer half-life agents.

ii. Long half-life/low potency: These drugs produce longer-lasting effects throughout the day, and although withdrawal symptoms may be less pronounced, they do occur. Interdose breakthrough symptoms are less likely; however, more “hangover” symptoms occur in the morning. These agents can accumulate in elderly patients.

iii. Table 11 compares the half-lives and potencies of the five main/most commonly prescribed benzodiazepines.

### Table 11. Half-lives and Potency of the Most Commonly Prescribed Benzodiazepines

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life (hours)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (Xanax)</td>
<td>6–12</td>
<td>0.5</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>5–30 (act. met.)</td>
<td>25</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>20–50</td>
<td>0.5</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>20–100 (act. met.)</td>
<td>10</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>10–18</td>
<td>1</td>
</tr>
</tbody>
</table>

act. met. = active metabolite.

b. The primary issues associated with benzodiazepines are tolerance and dependence. Tolerance of the hypnotic actions occurs within days. Dependence occurs within weeks to months of continued use. Abrupt cessation can lead to withdrawal problems. For this reason, it is generally recommended that treatment periods be restricted to 3–4 months, or about the time of an adequate trial on an antidepressant. After this time, the patient is tapered off the drug to avoid withdrawal and supplementation with other agents. Benzodiazepine tapers can take months to more than 1 year to complete. In practice, many of these patients go on to use these drugs for long periods. Often, these patients are not in remission, despite treatment with maintenance medications. In patients with a history of substance abuse or risk factors for substance abuse, the situation is different. In these patients, try to avoid the use of benzodiazepines because patients may begin to show an abusive pattern of use.

2. Antidepressants: SSRIs are also effective for several anxiety disorders. They are the agents of choice for long term treatment of anxiety disorders. Venlafaxine has been approved for the treatment of generalized anxiety and social anxiety disorders. Duloxetine is also approved for GAD. Some initial symptoms may be improved within days, but the full benefit of treatment may take weeks, as for depression treatment. Tricyclic antidepressants have preventive efficacy for panic disorder and anxiolytic activity. **Important note:** About 25% of these patients experience a hyper-stimulatory response to antidepressants, which can be confused with a worsening of the anxiety symptoms. This response is more common when therapy is first begun. Using low doses at first can help. Antidepressants can also be helpful for anxiety that accompanies depression.
3. Buspirone: This drug has anxiolytic properties, but clinicians’ opinions are divided on its real value in treating GAD. It has little efficacy for other anxiety disorders. The main drawback to buspirone is its long onset of action (weeks). In the meantime, the anxiety must be covered with another agent. Some clinicians will use short-term benzodiazepines as a bridge until buspirone takes effect.

4. Miscellaneous agents
   a. β-Blockers are sometimes used to block the peripheral symptoms of panic disorder or performance anxiety.
   b. MAOIs can be effective for the treatment of panic disorder when the patient also has atypical depression. However, these drugs are seldom used because of the potential for serious adverse effects.
   c. Antihistamines with sedating properties (e.g., hydroxyzine) can help reduce physical symptoms of anxiety.
   d. Barbiturates are seldom used. They are often less effective and can be lethal if taken in overdose.
   e. Antipsychotics are not considered first-line agents for the treatment of anxiety disorders. Selected SGAs can be useful as add-on therapy for OCD, GAD, and PTSD.

5. CBT should be an integral part of any therapeutic plan for treating anxiety disorders.

C. Recommended Therapy for Specific Anxiety Disorders

1. Generalized anxiety disorder
   a. Antidepressants: These are considered first-line agents. These include the SSRIs (escitalopram, paroxetine, and sertraline), the SNRIs (duloxetine and venlafaxine), and imipramine.
   b. Benzodiazepines: This class of drugs is rapidly effective; if possible, try to discontinue in 3–4 months, or once the patient has remittance of symptoms. Long-term therapy is common but not recommended. Benzodiazepines can be taken in combination with either antidepressants or buspirone as a bridge until these drugs start to take effect. They are more effective against somatic symptoms than against the underlying psychic pathology.
   c. Buspirone: Good when benzodiazepines should be avoided (e.g., in patients with a history of substance abuse); takes 2–4 weeks to be effective.
   d. Pregabalin: Considered a second-line agent behind antidepressants. Limited data suggest comparable efficacy with venlafaxine and benzodiazepines.
   e. CBT or another type of psychotherapy should generally be included with pharmacotherapy.
   f. In treatment-refractory patients, augmentation with quetiapine, olanzapine, or risperidone can be tried. Valproate also shows promise.

2. Panic disorder
   a. Antidepressants: First-line therapy. These include the SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), venlafaxine, and duloxetine.
   b. Benzodiazepines: High-potency agents; effective; rapid onset.
   c. Not effective: Buspirone, β-blockers, antihistamines, antipsychotics, bupropion, trazodone.
   d. CBT and other psychotherapies are effective.
   e. Patients with panic disorder tend to have a higher sensitivity to physical symptoms. For this reason, these patients should be initiated on low doses of antidepressants—as low 25 mg of sertraline or 5 mg of paroxetine.

3. Obsessive-compulsive disorder
   a. Serotonergic agents are effective—SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and clomipramine.
   b. CBT may be effective, but it is secondary to pharmacotherapy.
   c. Alone, SSRIs often fail to control OCD completely. Not many other drugs help. Augmentation with haloperidol or an SGA (olanzapine, quetiapine, or risperidone) may help. In general, high doses need to be used.
4. Posttraumatic stress disorder
   a. SSRIs (fluoxetine, sertraline, and paroxetine) are considered first-line agents.
   b. Augment with other agents to treat specific symptoms (e.g., intermittent explosive behavior with β-blockers or mood stabilizers).
      1. Prazosin is used to treat PTSD-associated nightmares.
      2. Anticonvulsants for aggression, anger, and depression (valproic acid, carbamazepine, lamotrigine, topiramate)
      3. Atypical antipsychotics for psychotic symptoms (olanzapine, quetiapine, risperidone)
   c. Benzodiazepines are not effective.
   d. As with all other anxiety disorders, CBT is integral.
5. Social anxiety disorder
   a. CBT is the most important modality.
   b. Antidepressants: First-line medication for treatment; SSRIs (escitalopram, fluvoxamine, paroxetine, sertraline) and venlafaxine. Response to antidepressants tends to be slow (up to 12 weeks) and has a flat dose-response curve.
   c. Clonazepam may be used as an adjunct.
   d. Gabapentin and pregabalin
6. Specific phobias
   a. Not treated with medication
   b. Systematic desensitization and other behavioral approaches often effective

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**Patient Cases**

*Questions 16–18 pertain to the following case:*

C.D. is a 38-year-old kindergarten teacher who presents to the clinic today with noticeable dark circles under her eyes. She has difficulty with sleep, mainly with staying asleep. It takes her about 20 minutes to fall asleep, but after about 2 hours, she wakes up and cannot fall asleep again for several hours. This pattern has taken a toll on her job, and she feels tired all the time. She once took diphenhydramine for sleep but had to miss work because of extreme drowsiness in the morning. She wonders whether there are any other medications she can take. Her other medical problems include hypothyroidism (levothyroxine 125 mcg at bedtime), hypertension (hydrochlorothiazide 25 mg in the morning), chronic back pain (ibuprofen 800 mg three times daily), and MDD (citalopram 20 mg in the morning).

16. Which agent is most likely contributing to C.D.’s insomnia?
   A. Citalopram.
   B. Hydrochlorothiazide.
   C. Ibuprofen.
   D. Levothyroxine.

17. Which medication used for insomnia is most appropriate to recommend for C.D.?
   A. Eszopiclone.
   B. Trazodone.
   C. Temazepam.
   D. Zaleplon.
Patient Cases (continued)

18. Which is the best example of an adverse effect that should concern C.D. when using zolpidem?
   A. Orthostasis.
   B. Disorientation.
   C. Abnormal behaviors while asleep.
   D. Seizures with high doses of the drug.

V. INSOMNIA

A. Normal Sleep Patterns and Neurochemistry/Physiology of Sleep
   1. We spend about one-third of our lives asleep. The amount of sleep required varies from individual to individual and changes with age.
   2. Sleep difficulties are common, with up to 35% of the population affected. Of interest, 4%–5% of the population may experience hypersomnia.
   3. People with sleep problems usually experience one or more of the following: insomnia, daytime sleepiness, or abnormal sleep behaviors.
   4. The sleep-wake cycle in humans usually lasts 25 hours, which means that with the 24-hour day-night cycle of the earth’s rotation, there must be some internal clock resetting. This resetting is accomplished by cues such as clocks and daylight, which tell the time of day.
   5. The neural networks regulating sleep-wake cycles are located in the brainstem, basal forebrain, and hypothalamus, with projections to the cortex and thalamus.
   6. The reticular activating system maintains wakefulness, and when activity here declines, sleep occurs.
   7. Several neurotransmitters are involved in the sleep-wake cycle. Norepinephrine, acetylcholine, histamine, and neuropeptides operate in the hypothalamus during wakefulness. Neuronal systems in the raphe nuclei, solitary tract, ventricular thalamus, anterior hypothalamus, and basal forebrain promote sleep. As the reticular activating system slows down, serotonin neurotransmission in the raphe nuclei reduces sensory input and inhibits motor activity. Norepinephrine is involved in dreaming, whereas serotonin is active during non-dreaming sleep.
   8. A lot of brain activity occurs during sleep; simultaneous electroencephalograms, electro-oculograms, and electromyograms characterize sleep stages. These are used to measure sleep latency (time to sleep onset), number of awakenings, number of stage shifts during the night, and latency to rapid eye movement (REM). These recordings are termed polysomnography. Stages are as follows:

Table 12. Sleep Stages

<table>
<thead>
<tr>
<th>State</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wakefulness</td>
<td>Low-voltage EEG, random eye movements, high muscle tone</td>
</tr>
<tr>
<td>Non-REM sleep</td>
<td>Low muscle tone, few eye movements</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Transition between wakefulness and sleep, low-voltage desynchronized EEG, lasts 0.5–7.0 minute</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Low-voltage EEG with sleep spindles and K-complexes</td>
</tr>
<tr>
<td>Stages 3 and 4</td>
<td>High-amplitude, slow-wave EEG, “delta sleep”</td>
</tr>
<tr>
<td>REM sleep</td>
<td>Low-voltage, mixed-frequency EEG, low muscle tone, REMs, autonomic fluctuations in heart rate and perspiration, and dreaming reported in 80%–90% of subjects</td>
</tr>
</tbody>
</table>

EEG = electroencephalogram; REM = rapid eye movement.
9. Sleep architecture is cyclic. Passing from wakefulness to stage 4 non-REM sleep takes about 45 minutes in young adults. Rapid eye movement usually occurs within 90 minutes of falling asleep; at first, REM lasts 5–7 minutes, but it gets progressively longer through the night. The sleep cycle (non-REM stages 1–4 and REM), which lasts about 70–120 minutes, is repeated four to six times a night. The typical young adult spends about 75% of his or her time in non-REM.

10. Sleep patterns change with age. Elderly patients experience less delta sleep, REM sleep, and total sleep time. They have more nocturnal awakenings and total time awake at night. The incidence of sleep pathology may be as high as 40%.

B. Sleep Disorders

1. The DSM-5 recognizes several sleep-wake disturbances: insomnia disorder, hypersomnia disorder, narcolepsy, obstructive sleep apnea, hypopnea, central sleep apnea, sleep-related hypoventilation, circadian rhythm sleep-wake disorders, non-REM sleep arousal disorders, nightmare disorder, REM sleep behavior disorder, restless legs syndrome, substance/medication-induced sleep disorder, and several other or unspecified sleep-wake disorders.

2. Insomnia

a. Insomnia is defined as an inability to initiate or maintain sleep, and it can be associated with problems during the daytime. About one-third of the U.S. population experiences insomnia, with half of those saying it is serious.

b. More than 40% of those suffering from insomnia self-medicate with over-the-counter medications (discussed below) or with other substances (e.g., alcohol).

c. Insomnia can be classified according to symptom duration as follows.

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration (weeks)</th>
<th>Likely Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient</td>
<td>&lt; 1</td>
<td>Acute situational or environmental stressors</td>
</tr>
<tr>
<td>Short term</td>
<td>&lt; 4</td>
<td>Continued personal stress</td>
</tr>
<tr>
<td>Chronic</td>
<td>&gt; 4</td>
<td>Psychiatric illness, substance abuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behavioral causes (poor sleep hygiene)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical causes, primary sleep disorder (e.g., sleep apnea, restless legs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>syndrome; these are no longer recognized by the DSM-V as insomnia</td>
</tr>
</tbody>
</table>

d. Transient insomnia is most often associated with acute stressors. It resolves once the acute stressors are removed. Pharmacotherapy may be used for a few days until the situation resolves.

e. Short-term insomnia is also most often associated with an acute stressor, but it is ongoing. Here, it is important to initiate good sleep hygiene (as below) and avoid stimulants such as caffeine. Pharmacotherapy may be indicated, especially if on an intermittent basis (e.g., skip it after 2 or 3 good nights of sleep). Therapy for 7–10 days is usually sufficient.

f. Chronic insomnia should be carefully evaluated for an underlying medical or psychiatric cause. If a cause is not present, a common type of chronic insomnia is chronic psychophysiological insomnia, which is a behavioral problem. The person has usually developed poor sleep hygiene, and the bedroom is associated with an alerting response. Behavioral therapy is important, but pharmacotherapy can be useful in short courses and intermittently. The development of chronic insomnia is a complex process and can be difficult to treat. Pharmacotherapy can be part of the overall treatment approach, but there is no consensus about how effective it is when used long term. Ramelteon, eszopiclone, and zolpidem controlled release all contain language in the package labels suggesting they can be used chronically.
g. The evaluation of insomnia should include an assessment of medical and psychiatric status. Medical causes are many and include thyroid disease and therapy with medications that can interfere with sleep. Several psychiatric conditions can interfere with sleep, including affective and anxiety disorders.

h. For all types of insomnia, patients can be instructed about good sleep hygiene. These principles are listed below:
   i. Maintain regular bedtimes and awakenings.
   ii. Do not go to bed unless you are sleepy.
   iii. Sleep long enough to avoid feeling tired, but no more.
   iv. Optimize the bedroom conditions (e.g., light, temperature, noise).
   v. Develop a bedtime ritual that allows you to unwind.
   vi. If you cannot go to sleep, or if you awaken and cannot go back to sleep, do not stay in bed more than 15–20 minutes; get up and do something else until you are sleepy.
   vii. Do not go to bed hungry, but do not stuff yourself before bed; try a small snack.
   viii. Avoid activities in the bedroom except for sleeping and sex.
   ix. Do not lie there and watch the clock; get one without a luminous dial.
   x. Avoid naps during the day.
   xi. Avoid stimulants such as caffeine and nicotine throughout the day.
   xii. Avoid alcohol because it can lead to “fragmented” sleep.
   xiii. Exercise regularly during the day, but not close to bedtime.

C. Pharmacotherapy of Insomnia

1. Pharmacotherapy is indicated for all forms of insomnia as long as it is part of an overall plan to deal with the causes and is used for well-defined periods. It should be considered adjunctive therapy only for short-term or chronic insomnia.

2. Agents that can depress respiration should be avoided in patients with respiratory disorders, a history of substance abuse, or obstructive sleep apnea. Ramelteon should be avoided in patients with severe sleep apnea.

3. There are several classes of sedative-hypnotics: barbiturates, which are no longer indicated; nonbarbiturates (e.g., chloral hydrate), which have only limited indications; benzodiazepines; and the non-benzodiazepines zolpidem, zaleplon, and eszopiclone, which are often used in clinical practice. Ramelteon is a melatonin receptor 1 and melatonin receptor 2 agonist. Suvorexant is an orexin receptor antagonist.

4. Benzodiazepines: In general, they are safe, effective, and well tolerated by most patients, but they are not considered first line. Although all members of this class can be used as sedatives, only five are FDA approved and marketed as such. These five are primarily used as sedative-hypnotics because they are rapidly absorbed and produce central nervous system actions more quickly than most anxiety agents. The sedative-hypnotic benzodiazepines are listed in Table 15. They are primarily differentiated by their onset of action and half-life in the body. According to their half-life, they are classified as short acting (half-life less than 6 hours), intermediate acting (half-life 6–24 hours), and long acting (half-life more than 24 hours). These are important parameters when selecting therapy. For instance, someone with problems initiating sleep would most likely benefit from an agent with a quick onset but short duration of action. Someone with problems maintaining sleep in the middle of the night might respond better to a drug with a longer half-life. The following table compares the benzodiazepines available in the United States.
Table 14. Benzodiazepines for Insomnia

<table>
<thead>
<tr>
<th>Drug (Trade)</th>
<th>Usual Dose (mg)</th>
<th>Half-life (hours)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triazolam (Halcion)</td>
<td>0.125–0.25</td>
<td>2–6</td>
<td>Short</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>15–30</td>
<td>8–20</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Estazolam (ProSom)</td>
<td>1–2</td>
<td>8–24</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>15–30</td>
<td>48–120</td>
<td>Long</td>
</tr>
<tr>
<td>Quazepam (Doral)</td>
<td>7.5–15</td>
<td>48–120</td>
<td>Long</td>
</tr>
</tbody>
</table>

5. These drugs are usually well tolerated. However, several problems still exist.
   a. Tolerance: Tolerance can develop, particularly when the drugs are used consistently for long periods. These drugs are not indicated for chronic use; however, newer evidence is emerging that they may be effective for longer periods than originally thought. Most are effective for 2–4 weeks and, in some cases, longer. An intermittent pattern of use can reduce the development of tolerance. In addition, most people without substance abuse histories do not escalate their doses.
   b. Residual daytime sedation: This is a common complaint of patients using these drugs. It is especially likely with agents having a long half-life. Dose is also an important factor; always use the lowest effective dose.
   c. Rebound insomnia: This can occur when the drug is discontinued abruptly. Insomnia is usually worse than baseline and usually lasts for 1–2 days; tapering the drug may minimize its effect. It is most common after the use of short- and intermediate-acting agents.
   d. Anterograde amnesia: All benzodiazepines appear to impair the acquisition and encoding of new information. They may also impair memory storage and recall. Dosage may be important.
   e. Be careful when using benzodiazepines in elderly patients because they can cause memory problems, increase the risk of falls, and accumulate (agents with a long half-life). Try to avoid use in this population. Idiosyncratic reactions can occur in elderly and pediatric populations with benzodiazepine use.
   f. Withdrawal: Physical dependence will occur if these agents are used long enough. Symptoms of withdrawal include worsening insomnia, anxiety, muscle twitches, photophobia, tinnitus, auditory and visual hypersensitivity, and seizures. Minimize by gradually tapering the drug at discontinuation.

Table 15. Nonbenzodiazepines for Insomnia

<table>
<thead>
<tr>
<th>Drug</th>
<th>t(_{1/2}) (hours)</th>
<th>Administration (minutes before sleep)</th>
<th>Indications</th>
<th>CDS Scheduling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sleep Onset</td>
<td>Sleep Maintenance</td>
<td>Chronic Therapy</td>
</tr>
<tr>
<td>Doxepin (Silenor)</td>
<td>15.3</td>
<td>30</td>
<td>X</td>
<td>Not controlled</td>
</tr>
<tr>
<td>Nordoxepin: 31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone (Lunesta)</td>
<td>6</td>
<td>Immediately</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ramelteon (Rozerem)</td>
<td>1.2</td>
<td>30</td>
<td>X</td>
<td>Not controlled</td>
</tr>
<tr>
<td>Suvorexant (Belsomra)</td>
<td>12</td>
<td>30</td>
<td>X</td>
<td>C-IV</td>
</tr>
</tbody>
</table>
Table 15. Nonbenzodiazepines for Insomnia (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>$t_{1/2}$ (hours)</th>
<th>Administration (minutes before sleep)</th>
<th>Indications</th>
<th>CDS Scheduling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sleep Onset</td>
<td>Sleep Maintenance</td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>1</td>
<td>Immediately</td>
<td>X</td>
<td>X (CR only)</td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>1.4–6.5 (see below)</td>
<td>Immediately</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

6. Doxepin (Silenor) is a tricyclic antidepressant indicated for the treatment of impaired sleep maintenance. The doses used are lower than those used to treat depression. Chances for morning effects are high due to the long half-life of both doxepin and its active metabolite, nordoxepin.

7. Eszopiclone (Lunesta): This non-benzodiazepine is a $\text{GABA}_A$ agonist. Its half-life is 6 hours, so morning effects could result if it is taken late in the night. This drug can be used for chronic insomnia. On May 1, 2014, the FDA reduced the starting dose to 1 mg in order to minimize the amount of next-day impairment. Patients should be counseled to use caution when driving or performing activities that require alertness, particularly with the 2–3 mg doses. It should be taken immediately before bed, and when the patient will be in bed for at least 7–8 hours.

8. Ramelteon (Rozerem): Melatonin agonist (no activity at the $\text{GABA}$ or benzodiazepine receptor). Duration is 2–5 hours. To date, there is no evidence that this melatonin agonist is associated with dependence or tolerance, and it may be used long term. This drug can be used long term for chronic insomnia. It is primarily metabolized by CYP 1A2, but inducers and inhibitors of 2C9 and 3A4 can also affect it.

9. Suvorexant (Belsomra) is a newly approved (August 2014) orexin receptor antagonist. It will be available in 2015. The neuropeptide orexin promotes wakefulness. By blocking the $\text{OX1R}$ and $\text{OX2R}$ receptors, suvorexant both decreases sleep latency and promotes sleep maintenance. It should be taken within 30 minutes of bedtime, and with at least 7 hours of sleep time. It is metabolized by CYP 3A4, and the dose must be decreased in patient taking concomitant 3A4 inhibitors. C-IV

10. Zaleplon: This is a non-benzodiazepine with a similar pharmacology to zolpidem (see below) and a very short half-life. For patients with sleep maintenance problems, it might not last as long. However, it has a shorter half-life (about 1 hour) and may cause fewer problems in the morning, especially if given late. It shortens onset to sleep, but does not prolong sleep time or number of awakenings. It is indicated only for short-term treatment of insomnia. It has been used in trials for up to 5 weeks. C-IV

11. Zolpidem: This non-benzodiazepine sedative-hypnotic modulates the $\text{GABA}_A$ receptor complex. C-IV
   
   a. Compared with benzodiazepines, zolpidem lacks anticonvulsant action, muscle-relaxant properties, and respiratory depressant effect; it also has a lower risk of tolerance and withdrawal. It should still be avoided in obstructive sleep apnea. It is a good choice for patients in whom benzodiazepines should be avoided.

   b. Zolpidem is available as an immediate release tablet (IR), controlled release tablet (CR), sublingual tablet (Edluar, Intermezzo), and sublingual spray (Zolpimist). The pharmacokinetics and indications vary based upon the dosing form. The sublingual spray has a shorter onset of action, but that of the sublingual tablet is comparable to both the IR and CR tablets.

   c. Indications vary by dosage form. All are indicated to decrease sleep latency. The CR tablets are indicated to improve sleep maintenance and can be used for longer term therapy. Intermezzo is indicated as a “prn” treatment for patient who have difficulty falling back to sleep, so long as $\geq 4$ hours remain.
d. The FDA has reduced the dosing recommendations to limit next day impairment. The dosing differs based upon the gender and degree of debility. For women, the nightly dose is 5 mg (IR) or 6.25 mg (CR). For men, it is 5-10 mg (IR) or 6.25-12.5 mg (CR). Debilitated patients should receive 5 mg (IR) or 6.25 mg (CR). Patients should be maintained on the lowest dose needed to benefit.

12. Patients should be warned about the potential risk of engaging in abnormal activities while asleep when taking sedative-hypnotics. Such behaviors may include driving, eating, having sex, or talking on the phone while asleep (with amnesia for the event). Other cautions include anaphylaxis and decreased respiratory drive.

13. Taking any of the agents listed in Table with food can delay onset of effects, thus prolonging the time to onset of sleep and increasing the risk for hangover effects in longer acting agents. Doxepin should be separated from meals by 3 hours.

14. Over-the-counter medications: These are most often antihistamines (doxylamine or diphenhydramine) that are both sedating and anticholinergic. They are possibly effective, but not as effective as benzodiazepines. Their regular use is not recommended. In fact, some data suggest that they do not maintain efficacy beyond a few days. They are associated with a higher incidence of daytime sedation than short- or intermediate-acting benzodiazepines. Diphenhydramine has been a popular agent when benzodiazepines were contraindicated. However, caution should be used in elderly patients because an anticholinergic action can worsen dementia or other medical conditions. In addition, it should not be administered with the cholinesterase inhibitors used for Alzheimer disease.

15. Other non-benzodiazepines: In some situations, antidepressants such as trazodone may be used as sedative-hypnotics. These can be effective, and often, the dose required is lower than that used for depression. However, efficacy has not been fully established through clinical trials. Trazodone has been popular for managing insomnia caused by SSRI antidepressants (see discussion in Depression section). It is also popular by itself as a sleep agent because the potential for dependence is low. However, it is associated with considerable adverse effects, and the data for long-term use are scant.

### Patient Cases

**Questions 19–22 pertain to the following case:**

L.M. is a 50-year-old patient with a 25-year history of alcohol dependence who was found unconscious after his last drinking binge. He was first admitted to the medical unit for alcohol withdrawal symptoms before being transferred to the substance dependence unit. His last drink was 6 hours ago, and fluids have been started. He has had three alcohol withdrawal seizures in the past and an episode of delirium tremens. He also has significant hepatitis, and liver function tests show aspartate aminotransferase (AST) of 220 IU/L and alanine aminotransferase (ALT) of 200 IU/L.

19. Which symptom are you most likely to observe in the medical unit?
   - A. Alcohol craving.
   - B. Delirium tremens.
   - C. Increased heart rate.
   - D. Seizures.

20. Which agent is best for alcohol withdrawal symptoms in L.M. for intramuscular administration?
   - A. Chlordiazepoxide.
   - B. Clonazepam.
   - C. Diazepam.
   - D. Lorazepam.
VI. SUBSTANCE ABUSE

A. Alcohol
1. Acute Withdrawal
   a. Characteristic symptoms occur after alcohol discontinuation. The symptoms that develop, how quickly they develop, and the degree of severity depend on the level of alcohol abuse and a person’s characteristics. Not all patients develop delirium tremens, nor do all develop seizures. However, it is difficult to predict, so detoxification should always be supervised. A history of alcohol withdrawal problems suggests that inpatient detoxification is indicated.
   b. Table 16 lists the stages of acute alcohol withdrawal.

c. Delirium tremens, which can be life threatening, should be considered a potential medical emergency and treated promptly.

d. The seizures that occur are often difficult to control. Status epilepticus can develop; thus, it is important to ensure that these patients have intravenous access. Benzodiazepines are first line for seizure prevention in alcohol withdrawal compared with other anticonvulsants.

2. Treatment of Acute Alcohol Withdrawal
   a. The degree of symptoms and the resulting level of treatment should be individualized, and an accurate history regarding amount, duration, and past withdrawal symptoms including seizures and delirium tremens should guide treatment. If it is believed that complications may arise, treatment should take place in an inpatient setting.
b. In determining the level of intervention required, the severity of symptoms is usually assessed. The more severe the symptoms are, the more aggressive the intervention(s).

c. The principle of cross-tolerance is used to advantage in the prevention and treatment of withdrawal symptoms. Benzodiazepines can eliminate many manifestations of withdrawal and are much easier to control with respect to dosing.

i. Intermittent dosing: Using this regimen, patients are assessed for the severity of withdrawal symptoms; then, the benzodiazepine dose is adjusted to that level. This is probably the most prevalent way of treating these patients.

ii. Scheduled dosing: Another strategy is to begin a scheduled dose of benzodiazepine on admission, give it regularly, and then taper it down for 3–4 days until symptoms have abated.

iii. Loading-dose (front loaded) protocol: A new approach during recent years uses a loading-dose strategy for diazepam. Diazepam is given in a dose of 10–20 mg every 1–2 hours until the symptoms of withdrawal are alleviated. Most patients will need two or three doses, especially those with a history of seizures during withdrawal, in which case three doses should be used. The half-life of diazepam is long, and most patients will not need subsequent doses in this protocol once symptoms are relieved. Of course, patients should be monitored closely.

iv. Table 17 lists the benzodiazepines that may be used. Chlordiazepoxide has the status of the “classic” drug, possibly the oldest, and it can be given either orally or parenterally. However, it has no proven advantages over the other agents; in fact, its long half-life may cause unnecessary sedation. However, for patients with a high risk of withdrawal seizures or delirium tremens, a long-acting benzodiazepine may be preferable. If a shorter-acting agent is used, a round-the-clock schedule would be ideal for high-risk patients. Lorazepam is also safe to administer in patients with liver disease.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (Ativan)</td>
<td>1–2 mg PO/IV/IM</td>
<td>Good for general use; less of a problem with liver disease; IM/IV available</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>5–20 mg PO/IV/IM</td>
<td>Use lower dose if liver disease is present; may administer by slow IV; can use a loading-dose strategy</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>25–100 mg PO/IV</td>
<td>Long acting; be careful if liver disease is present</td>
</tr>
</tbody>
</table>

IM administration of diazepam is unreliable. IM = intramuscular(ly); IV = intravenous(ly); PO = orally.

d. Nutritional considerations

i. Thiamine: This should be given to all patients to prevent Wernicke-Korsakoff syndrome—100 mg intramuscularly on admission and then orally for 3 days; always give the first dose before glucose because it is a cofactor for the metabolism of glucose.

ii. Magnesium: Assess by serum chemistry; if low, give intravenous supplement.

iii. Electrolytes: Assess by serum chemistry and add to intravenous solutions as indicated (e.g., potassium).

iv. Vitamins: These patients are usually undernourished; a good multivitamin may be indicated (folic acid and vitamin B12 should be monitored).

e. Fluid therapy: The patient may initially be overhydrated, but usually, fluid deficit will follow; replace fluids, usually with intravenous 5% dextrose solution with half-normal saline plus other electrolytes (e.g., potassium, phosphate). 

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**Table 17. Benzodiazepines in the Treatment of Acute Alcohol Withdrawal**
f. Hallucinations: Benzodiazepine will usually manage hallucinations effectively; if not, give haloperidol; however, be cautious because haloperidol can lower the seizure threshold.

g. Seizures: Benzodiazepine will usually prevent seizures. Higher doses (and/or increased frequency) of benzodiazepines can be used if the patient has a history of seizures. If a seizure occurs during withdrawal, increasing the benzodiazepine dose and slowing the taper are options. Other antiepileptics may be used to treat status epilepticus, but their efficacy varies.

h. Other agents
   i. β-Blockers: These agents help with vital signs and blood pressure.
   ii. α-Agonists (e.g., clonidine): These agents may help with some of the withdrawal symptoms.

3. Chronic Therapy
   a. Disulfiram: This drug blocks acetaldehyde dehydrogenase, and if alcohol is used with it, the person will develop symptoms that include nausea/vomiting, flushing, and headache, among others. Adherence is critical, and disulfiram is usually reserved for patients with considerable motivation for adherence. Caution should be exercised in patients with liver disease, particularly if is severe or the patient has cirrhosis. Disulfiram has been associated with hepatotoxicity, although it is not known whether patients with existing liver disease are at an increased risk.

   b. Naltrexone: This drug can also be used chronically and has been shown to reduce cravings. If used, it should be combined with CBT. Liver toxicity is associated with this drug. The extended-release injectable suspension (Vivitrol) is available in an intramuscular formulation and is approved for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting before treatment initiation.

   c. Acamprosate (Campral): This drug is a structural analog of GABA. It, too, reduces cravings. It is not metabolized by the liver; however, it must be taken three times daily.

B. Opioid Dependence
   1. In 2013, 1.5 million people used prescription pain relievers for nonmedical reasons. The majority (53%) get their drugs free from friends or relatives. The number of people who received treatment for nonmedical use of prescription pain relievers was 746,000, up from 360,000 in 2002. In 2012, 16,007 deaths due to overdose with opioid analgesics occurred, totally 72% of all deaths due to overdoses with pharmaceuticals.

   2. The potential for abuse led the DEA to reclassify products containing hydrocodone and acetaminophen from C-III to C-II, effective October 6, 2014.

   3. Opioid withdrawal is not life-threatening in absence of concomitant medical conditions. Early symptoms may resemble flu and include agitation, anxiety, muscle aches, yawning, sweating, rhinorrhea, and lacrimation. Later symptoms include abdominal cramping, diarrhea, piloerection, dilated pupils, nausea, and vomiting.

      Pharmacologic therapies for opioid addiction include maintenance therapy with methadone, an opioid agonist; antagonist therapy with naltrexone; detoxification with medications given in rapid taper (e.g., methadone, buprenorphine, or clonidine) to prepare the patient for antagonist or counseling therapy; and partial agonist therapy with buprenorphine or buprenorphine/naloxone.

   4. The use of buprenorphine came about as a result of the Drug Abuse Treatment Act of 2000 (DATA), which allows qualifying physicians to apply for a waiver to treat opioid addiction outside an opioid treatment program using schedule III, IV, and V medications that are FDA approved for this indication.

      a. Only two formulations that qualify under DATA 2000 are FDA approved for opioid dependence: buprenorphine (available as sublingual tablets [Subutex]) and buprenorphine/naloxone (available in 4:1 ratio dosing increments as sublingual tablets [Zubsolv], sublingual film [Suboxone], and buccal film [Bunavail]).
b. Buprenorphine is a partial agonist at the opioid mu receptor and an antagonist of the kappa receptor. The mu receptor binding affinity is higher than that of full opioid agonists with a lower intrinsic activity. Thus, it will displace morphine, methadone, and other opioid drugs but only gives a fraction of effect that levels out with increasing doses—a ceiling effect. This allows patients enough effect to “feel normal” but minimizes functional impairment. It also makes the drug safer in overdose situations. At high enough doses, the kappa antagonist properties could precipitate withdrawal.

c. The addition of naloxone reduces abuse potential because naloxone is less potent when given sublingually than by injection. Thus, if the medication is used as intended (sublingually), the likelihood of withdrawal symptoms is low as opposed to dissolving and injecting it.

5. Treatment with buprenorphine involves three phases: induction, stabilization, and maintenance. Buprenorphine/naloxone is the preferred agent for most patients, including those taking short-acting opioids (hydromorphone, oxycodone, heroin). Patients taking long-acting opioids (methadone, long-acting morphine, long-acting oxycodone) should be tapered to methadone 30 mg/day or less or the equivalent, and transitioned to buprenorphine first. It is recommended that these patients be switched to the combination after no more than 2 days on buprenorphine monotherapy.

a. Patients should not be intoxicated or feeling effects from their last dose of opioid (~12–24 hours since the last dose of short-acting opioid). They must also be screened for other substance abuse and for appropriateness of buprenorphine therapy. Patients may feel like they are going through early stages of withdrawal. In these cases, the opioid receptors are not fully occupied, and the buprenorphine is less likely to induce withdrawal.

b. Patients need to receive concomitant counseling and nonpharmacologic treatment support during treatment. Part of the DATA 2000 waiver requires that physicians be able to refer the patient to appropriate supportive services. Counseling should take all psychosocial factors into account.

c. Induction phase: Find the minimum dose of buprenorphine that minimizes cravings for opioids but prevents withdrawal symptoms. The first dose should be given in the office and the patient observed for 2 hours. The patient is given the 4/1 dose of buprenorphine/naloxone. If withdrawal symptoms are not relieved or return before the 2-hour period, a second dose of 4/1 is given, and the daily dose is established at 8/2. The dose established during the induction phase depends on the presence of withdrawal symptoms on subsequent days, to a maximum of 32/8.

d. Stabilization phase: Reached when the patient is without withdrawal symptoms, is not experiencing side effects of buprenorphine/naloxone, and no longer has uncontrollable symptoms of craving. Toxicology screens can be used to verify that the patient is not using opioids. Patients should be seen weekly until stable. Doses can be adjusted in 2/0.5 to 4/1 increments. Most patients are maintained on 16/4–24/6.

e. Maintenance: Once the minimum dose needed to maintain abstinence is reached, the buprenorphine/naloxone therapy can be maintained indefinitely. Nonpharmacologic modalities should continue during this time.

f. Discontinuation: This should be considered only if the patient is psychologically and medically stable, is able to maintain a drug-free lifestyle, and no longer feels the drug is necessary to remain abstinent. The medication should be tapered slowly to avoid withdrawal symptoms.

6. Buprenorphine is metabolized by CYP3A4. Use caution with other medications that either induce or inhibit 3A4.

C. Tobacco Dependence

1. Tobacco use is the top cause of preventable morbidity and mortality.

2. It increases the risk of cardiovascular disease (including stroke), chronic obstructive pulmonary disease, and cancer (both lung and nonlung).
3. According to the 2012–2013 National Annual Tobacco Survey, 21.3% of Americans use a tobacco product every day or on most days, and 19.2% used some form of combustible tobacco product. Cigarettes are the most commonly used product. Rates have greatly declined over the past decade. There are more former smokers than current smokers.

4. Smoking cessation counseling is not consistently offered and tends to be directed to patients with tobacco-related conditions. Interventions lasting as little as 3 minutes make a difference. Patient counseling can help prime patients who are not willing to quit to consider it and act on it in the future.

5. As of January 2015, the Joint Commission will require inpatient psychiatric services to screen for tobacco use (TOB-1), offer or provide treatment for tobacco dependence (TOB-2), and provide or offer treatment for tobacco dependence at discharge (TOB-3).

6. It takes an average of seven attempts for a patient to quit successfully.

7. Willingness to quit should be assessed via the five A’s: ask about tobacco use, advise to quit, assess willingness to attempt to quit, assist in quit attempt, and arrange for follow-up.

8. Motivational interviewing is a successful technique that can help identify barriers to change and help the patient overcome them.

9. The five R’s can be used to increase motivation to quit: relevance, risks, rewards, roadblocks, and repetition.

10. Quit lines such as 1-800-QUIT-NOW can facilitate attempts.

11. Seven pharmacologic agents (five nicotine and two nonnicotine) are available to help. They should be used with nonpharmacologic modalities to increase the success of quitting.


13. Nicotine replacement therapy (NRT): All forms are equally efficacious. Patients should be advised to stop smoking completely before initiating. It comes in the following forms:

   a. Patch: For patients who smoke more than 10 cigarettes/day, start with 21 mg/day for 2 weeks, then 14 mg/day for 2 weeks, then 7 mg/day for 2 weeks. Those who smoke 10 cigarettes/day or less, start with 14 mg/day for 6 weeks, then 7 mg/day for 2 weeks. Patches may be used for longer periods of time if needed to improve success. It is recommended to change the patch upon awakening every day. Rotate sites.

   b. Gum: The gum should be chewed until a “peppery” or flavored taste develops, then “park” the gum between the cheek and gum to facilitate buccal absorption. The gum should be chewed and parked for 30 minutes or until the flavor is gone. The maximum number of pieces of gum is 24 pieces in 24 hours. At least 9 pieces of gum should be used daily to increase the chances of quitting. Patients who smoke 25 cigarettes/day or more should use the 4-mg dose. Those who smoke fewer than 25 cigarettes should use the 2 mg dose. One piece of gum should be used every 1–2 hours for the first 6 weeks of therapy, followed by 1 piece every 2–4 hours for weeks 7–9, then 1 piece every 4–6 hours for weeks 10–12. Acidic beverages (e.g., coffee, juices, and soft drinks) interfere with buccal absorption and should be avoided at least 15 minutes before using the gum. Side effects include soreness, dyspepsia, hiccups, and jaw ache. They are usually mild and can be corrected with changes in chewing technique.

   c. Lozenge: Patients who smoke their first cigarette within 30 minutes of waking should use the 4-mg strength. Otherwise, the 2-mg dose is used. The lozenge should be dissolved in the mouth rather than being chewed or swallowed. The frequency of use and downward titration are the same as for the gum. Side effects are also similar. At least 9 lozenges should be used at the beginning to increase chances of quitting. Only 1 lozenge should be used at one time. No more than 5 lozenges within 6 hours, maximum 20 lozenges/24 hours.
d. Inhaler: Available by prescription only. Each puff delivers 4 mg. Each cartridge delivers 80 inhalations. The recommended dosing is 6–16 cartridges/day. The best results are obtained if the contents of the cartridges are continuously puffed over approximately 20 minutes. Recommended treatment length is 3 months, with reduction in frequency over the last 6–12 weeks. As with the gum and lozenges, patients should not drink acidic beverages or eat within 15 minutes of using the inhaler. Delivery decreases at less than 40°F, so the inhaler should be kept in an inner pocket in cold weather. The most common side effects are sore throat, coughing, and rhinitis. Inhalers should be avoided in patients with reactive airway diseases.

e. Nasal spray: Available by prescription only. The dose is 0.5 mg delivered to each nostril. One to two doses should be used hourly, up to 5 doses. The 24-hour maximum is 40 doses. At least 8 doses should be used at the start of therapy. Each bottle contains 100 doses. Recommended length of therapy is 3–6 months, with downward titration. Risk of dependency is higher than with other forms of nicotine replacement. Inhaling, sniffing, and swallowing can increase the risk of nasal irritation and so should be avoided when taking the spray. Nasal irritation can occur in up to 94% of patients. Although it can resolve, a significant number of patients may have it as much as 8 weeks into therapy. It is not recommended for use in patients with reactive airway diseases or nasal conditions.

f. Nicotine patches can be used with the as-needed dosage forms to increase the chances of quitting.

g. Patients with a history of cardiovascular disease can use nicotine replacement therapies.

h. The treatment of choice in pregnant women is nonpharmacologic. Nicotine has a pregnancy category D rating. NRT has not been shown to be effective in pregnant women.

14. Bupropion sustained release (SR): Bupropion SR should be initiated 7 days before the quit date. Treatment should last for at least 8 weeks but can be continued for up to 6 months to increase chances of quitting. It can also be combined with the nicotine patch if needed.

15. Varenicline: It is a nicotine receptor partial agonist. It blocks the effects of nicotine from smoking. It should be started 1 week before the quit day, although patients can choose to quit smoking up to 35 days after initiating varenicline. It should be continued for a total of 12 weeks. If the patient is successful at smoking cessation, it can be continued for another 12 weeks. Varenicline carries a black box warning for neuropsychiatric symptoms, including depression, suicidal ideation, suicide, psychosis, mood disturbance, and hostility. This can occur in patients with or without preexisting psychiatric conditions. It is associated with an increase in cardiovascular events, particularly in patients with pre-existing cardiovascular disease. It must be used with caution in patients with creatinine clearance less than 30 mL/min. Combining it with NRT increases side effects. It can be combined with bupropion.

16. Other agents used include clonidine and nortriptyline.

17. Patients who were unsuccessful in quitting on one form of pharmacologic therapy should be tried on a different method.
REFERENCES

Depression


Bipolar Disorder


Schizophrenia


Anxiety Disorders


Insomnia


2. Sateia M, Nowell P. Insomnia. Lancet 2004;364:1959-73. This is a good review of the pathophysiology and treatment of insomnia. It also includes a discussion of nondrug interventions.

Substance Abuse


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C
Paroxetine has the most interaction with this patient’s current medications because of its interaction with hydrocodone by inhibition of the CYP2D6 isoenzyme. This will result in a lack of analgesic effects from the opiate. Fluvoxamine is a CYP1A2 inhibitor that has no interaction with thiazides, metformin, or opiates. Citalopram has no appreciable effects on any of this patient’s medications. The effect of sertraline, although it may compete with that of hydromorphone (metabolite of hydrocodone) through CYP3A4, is less than that of paroxetine.

2. Answer: C
Mirtazapine is appropriate because it can improve this patient’s insomnia and poor appetite. In addition, mirtazapine does not have a drug-drug interaction with the patient’s current medications. Fluoxetine, bupropion, and venlafaxine would worsen her insomnia. Venlafaxine would worsen hypertension, and bupropion would worsen decreased appetite.

3. Answer: B
The citalopram dose should be increased to 40 mg/day because this patient has had some initial response to the drug (improvement in insomnia and appetite) but may not have reached the maximal tolerated dose. The patient has been taking citalopram for only 4 weeks, possibly at a subtherapeutic dose. Bupropion can be added later, after the patient has reached a maximal tolerated dose of citalopram for 6–8 weeks (which is a therapeutic trial). Switching SSRIs may also be an option after the maximal tolerated dose of citalopram is reached.

4. Answer: B
The patient still needs an antidepressant, and discontinuing citalopram without an alternative agent at 6 months is inappropriate. Bupropion can be added to treat the anorgasmia and may even provide augmentation effects. Switching to a different SSRI may also produce the same adverse effect because the anorgasmia appears to be caused by serotonergic activity. Switching to mirtazapine is not appropriate because the patient has had a therapeutic response and has been doing well for 6 months.

5. Answer: C
Lithium should be initiated to treat the current manic phase and prevent future episodes. Carbamazepine is effective for maintenance treatment but considered second or third line for acute mania. Divalproex is also good for maintenance treatment, but given this patient’s history of hepatitis C, it is not a good choice. Lamotrigine is also effective for maintenance but not effective for treating the patient’s current manic phase.

6. Answer: B
Coarse tremor may indicate lithium toxicity and would require an immediate evaluation of the patient’s lithium level. Lithium can cause hyperthyroidism, severe acne, and weight gain, but these can generally be managed with lifestyle modifications or medications.

7. Answer: C
This patient appears to be showing symptoms of lithium toxicity, and a lithium level should be ordered immediately. Certainly, medications that may worsen the condition (e.g., lisinopril, ibuprofen, zolpidem) may be discontinued later.

8. Answer: A
Benztropine or another anticholinergic should be given to reverse the symptoms of EPS (neck stiffness, extreme restlessness). Giving more antipsychotics only worsens the symptoms of EPS.

9. Answer: B
Risperidone has less risk of EPS than haloperidol/FGAs, but it has the greatest risk among SGAs. Risperidone is effective for negative symptoms, like other SGAs, and can be dosed once daily after reaching the target dose. However, for this patient with a significant history of nonadherence, the most likely reason for initiating risperidone is to eventually convert him to the long-acting injection formulation (Risperdal Consta), given twice a month.
10. **Answer: C**
Risperidone is more likely to cause EPS than other SGAs. Risperidone may cause some sedation but not appreciably so. Anticholinergic effects are minimal with risperidone. Although all antipsychotics can potentially cause QTc prolongation, they rarely cause problems in patients without risk factors.

11. **Answer: D**
Quetiapine is most appropriate given the patient’s history of dystonia and akathisia with haloperidol. Quetiapine has a lower risk of causing EPS than FGAs such as fluphenazine. Clozapine and olanzapine have low risks of EPS as well, but clozapine is reserved for treatment-resistant cases. Olanzapine is not preferred because of the significant metabolic risks in this young patient.

12. **Answer: A**
Paroxetine should be continued at this time because the patient is being successfully treated for depression, and paroxetine is considered a first-line agent for PTSD. Sertraline also treats PTSD, but there is no reason to discontinue paroxetine. Adding adjunctive agents such as lorazepam and buspirone is not indicated because it has been only 3 weeks since paroxetine was initiated.

13. **Answer: C**
Anticonvulsants such as divalproex sodium are often used to treat symptoms of irritability and aggression in patients with PTSD. Buspirone is generally ineffective for these symptoms of PTSD and is used for GAD. Clonazepam can be used for short periods for anxiety; however, it is generally not used to target these symptoms of aggression. Lithium may be able to control the mood lability, but it requires close monitoring.

14. **Answer: D**
Buspirone is not a benzodiazepine and does not have much dependence potential. Buspirone does not work in relieving nightmares, and it is dosed three times daily. It also takes about 2 weeks for the onset of effect.

15. **Answer: A**
Clomipramine is the most serotonergic drug of the choices provided and is highly effective for OCD.

16. **Answer: D**
The patient is taking levothyroxine at nighttime, which is most likely to be contributing to the insomnia. Hydrochlorothiazide and ibuprofen are not significantly associated with causing insomnia. Citalopram may contribute to insomnia in certain patients, but this patient is taking it in the morning, which decreases the risk.

17. **Answer: A**
The patient does not want a drug with significant daytime sedation, but she needs a drug that will help her stay asleep throughout the night. Eszopiclone is the best option. Trazodone has a long half-life that will help her stay asleep but has fewer efficacy data for insomnia. Temazepam causes daytime sedation. Zaleplon does not cause daytime sedation, but the short half-life of the drug will not help her stay asleep.

18. **Answer: C**
Zolpidem and other sedative-hypnotics have been associated with causing abnormal behaviors such as eating, driving, having sex, and talking on the telephone while asleep. Zolpidem may cause orthostasis and disorientation, but when taken appropriately, it does not cause significant problems. Zolpidem at high doses has been associated with seizures, but this patient does not have a history of drug abuse or of using high doses of medications.

19. **Answer: C**
The initial symptoms of alcohol withdrawal include hemodynamic instability such as elevated heart rate and blood pressure. Alcohol craving, delirium tremens, and seizures generally occur after 12 hours of being abstinent.

20. **Answer: D**
Lorazepam can be given intramuscularly and is appropriate because of the patient’s liver abnormalities. Lorazepam undergoes glucuronidation and does not rely on oxidative pathways for metabolism. Chlordiazepoxide and diazepam are not available in intramuscular formulations and should be avoided in patients with liver disease. Clonazepam is generally not used for alcohol withdrawal and not given intramuscularly.
21. **Answer: D**
Thiamine should be administered before fluids containing glucose to prevent Wernicke-Korsakoff syndrome. Folate, a multivitamin supplement, and $B_{12}$ are also helpful but can be given after fluids.

22. **Answer: A**
Given the patient’s liver disease, acamprosate is most appropriate because it does not rely on hepatic metabolism. Disulfiram and naltrexone are not generally recommended in patients with liver disease. Diazepam is not used for alcohol dependence but is used during alcohol withdrawal.
ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B
Fluoxetine has a side effect profile that most closely counteracts the patient’s symptoms. She additionally has anxiety, so the fluoxetine may concomitantly relieve her symptoms of anxiety and allow her to stop her benzodiazepine. Paroxetine can increase appetite and cause somnolence, as can mirtazapine. Although her suicidal ideation is intermittent and passive, desipramine could be fatal in an overdose situation.

2. Answer: B
Duloxetine is the best choice because it is also indicated for diabetic neuropathy. Although nortriptyline is also used to treat neuropathy, it is not a good choice in a patient with cardiovascular disease. It could also cause weight gain. Although bupropion is either weight neutral or can lead to some weight loss, the data are not strong for use in neuropathy. Sertraline is safe in this patient and could be used as an alternative to citalopram but has no utility in the treatment of neuropathy.

3. Answer: D
L.J. is experiencing serotonin syndrome (myoclonus, agitation, diaphoresis). The symptoms are probably caused by adding dextromethorphan to paroxetine. In addition to the serotonergic activity of both agents, paroxetine inhibits CYP2D6, which is responsible for metabolizing dextromethorphan. This further increases the serotonergic activity. None of the other choices represents a combination of serotonergic agents, nor do they interact in a fashion that would cause a rise in serotonergic activity.

4. Answer: C
H.G. is experiencing an acute depressive episode despite therapeutic lithium concentrations. He has been taking lithium long enough to derive any antidepressant effects. Quetiapine is FDA indicated for depression associated with bipolar disorder. Its onset of action is more rapid than that of lamotrigine, which requires a slow titration to reach therapeutic doses. Unlike for unipolar depression, data for aripiprazole suggest it is not effective for bipolar depression. The efficacy of antidepressants in treating bipolar disorder type I is questionable, and treatment with an SNRI could lead to a switch to mania.

5. Answer: A
H.K. is experiencing hypothyroidism, as indicated by her elevated thyroid-stimulating hormone (TSH). This is probably induced by her lithium. Although olanzapine can cause a metabolic syndrome with glucose intolerance and obesity, it would not cause an elevation in her TSH. Lithium-induced hypothyroidism is not dose-dependent, and the patient’s lithium level is on the lower side of the 0.6–1.0 mEq/L maintenance range. Yasmin (ethinyl estradiol/drospirenone) is not associated with elevations in TSH.

6. Answer: B
This patient has acute pancreatitis. Although the incidence is rare, divalproex can cause pancreatitis. Patients who develop pancreatitis on divalproex and resolve off it should not be rechallenged. Neither aripiprazole nor lamotrigine is associated with pancreatitis (although I.T.’s lamotrigine dose should have been lowered to prevent Stevens-Johnson syndrome). Despite the temporal relationship with prednisone, it is not likely to be contributing to the current clinical picture.

7. Answer: D
The symptoms most closely resemble akathisia. The treatment of choice is a lipophilic β-blocker such as propranolol. Benztrapine is an anticholinergic agent that can be used for other movement disorders, such as dystonias or Parkinsonian symptoms, but it is not effective for akathisia. Benzodiazepines might relieve some of the anxiety but will not treat the underlying problems. Dantrolene is used for neuroleptic malignant syndrome.

8. Answer: B
This patient is experiencing severe tardive dyskinesia. The symptoms involve the orofacial muscles and came on slowly after antipsychotics had been started. The symptoms improved with antipsychotic dose reduction. The antipsychotic of choice in patients with severe tardive dyskinesia is clozapine. Chlorpromazine is also a first-generation antipsychotic associated with tardive dyskinesia. Although risperidone is associated with less EPS, it can cause tardive dyskinesia. Quetiapine has a low incidence of tardive dyskinesia but would not be the agent of choice with severe tardive dyskinesia.
9. Answer: D
U.M. has diabetes, dyslipidemia, and obesity, all factors that contribute to metabolic syndrome. With her family history of early coronary artery disease, she would best be served by an antipsychotic with a low incidence of metabolic syndrome. Of the antipsychotics listed, ziprasidone is the best choice. Olanzapine is associated with one of the highest incidences of metabolic syndrome. Quetiapine has a lower incidence but can still cause metabolic abnormalities. Paliperidone, which is structurally related to risperidone, is also associated with an elevated incidence of galactorrhea.

10. Answer: A
N.Y. has panic disorder. Benzodiazepines treat the acute physical symptoms and fear that occur with panic disorder. SSRIs such as paroxetine are first-line treatment for preventing panic attacks but do not play a role in acute treatment. Buspirone is not effective for panic attacks. Hydroxyzine may offer some sedation but is ineffective to treat the underlying anxiety.

11. Answer: D
An antidepressant is the first-line treatment for generalized anxiety disorder (GAD). Venlafaxine is the agent of choice for several reasons. It has demonstrated efficacy against GAD. In addition, it may offer some relief against T.R.’s vasomotor symptoms. Fluoxetine is an effective choice for GAD but is a strong inhibitor of CYP2D6. This would decrease the efficacy of her tamoxifen. Bupropion is also an inhibitor of CYP2D6 and is not effective against most anxiety disorders. Pregabalin is sometimes used to treat GAD, but only as a second- or 3rd third-line agent.

12. Answer: B
O.P. primarily has difficulty with sleep onset and would benefit from an agent that would decrease sleep latency and not prolong sleep. Ramelteon is the only one of the listed agents that does this. Older adults can have difficulty with circadian rhythm, and a melatonin analog may help regulate this. It is also indicated for treatment of chronic insomnia if needed for a prolonged period. Although eszopiclone decreases time to sleep, it is also designed to improve sleep maintenance and may result in hangover effects. Suvorexant also treats sleep maintenance and could cause a hangover effect. Zolpidem received recent labeling changes for reduced doses and has reduced metabolism in older adults.

13. Answer: D
To avoid withdrawal symptoms, patients who are on long-acting opioids should be tapered to the equivalent of methadone 30 mg/day or less before being switched to a buprenorphine regimen. Starting a patient on buprenorphine at higher doses of methadone may precipitate withdrawal because of the higher binding affinity of buprenorphine for the mu receptor with less activity and the added antagonism at the kappa receptor. Patients on long-acting opioids such as methadone should be switched to buprenorphine monotherapy before being advanced to buprenorphine/naloxone. Naltrexone monotherapy is not appropriate because it can precipitate withdrawal.

14. Answer: D
C.H. has alcoholic hepatitis, as indicated by his AST and ALT values. Liver function is intact, as evidenced by his albumin, prothrombin time, and platelet values. Presumably this would improve with abstinence. Naltrexone can be given to patients with hepatic dysfunction. Hepatic function would need to be monitored. Disulfiram should be used with caution in patients with active liver disease. It also requires a strong commitment on the part of the patient to abstain from drinking. This patient has a history of several failed attempts. Acamprosate would need to be adjusted downward for the patient’s renal function. Chlordiazepoxide is used during acute alcohol detoxification but has no role in maintenance therapy.

15. Answer: A
J.Z.’s previous quit attempt with nicotine gum was probably unsuccessful because the gum strength (2 mg) and frequency of use (less than 9 pieces/day) were too low to support a successful attempt. Thus, his previous use of nicotine gum is not a true treatment failure. Nevertheless, he has concomitant depression, so bupropion is a reasonable choice. His MI is not a contraindication to using nicotine products and could be added to bupropion if monotherapy fails. Coronary artery disease is not a contraindication to varenicline therapy, but because bupropion has not been previously used, it should be tried first.