General Psychiatry

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Learning Objectives

1. Examine pharmacotherapeutic options for managing major depression, bipolar disorder, schizophrenia, anxiety disorders, insomnia, and substance use disorder.
2. Select a drug used to treat these disorders on the basis of its unique pharmacologic properties, therapeutic efficacy, adverse effects, and cognitive and behavioral effects.
3. Formulate a pharmacotherapeutic treatment plan for a patient with a diagnosis of major depression, bipolar disorder, schizophrenia, anxiety disorder, insomnia, or substance use disorder.

Abbreviations in This Chapter

ANC Absolute neutrophil count
CBT Cognitive behavioral therapy
DEA Drug Enforcement Agency
EPS Extrapyramidal symptoms
FGA First-generation antipsychotic
GAD Generalized anxiety disorder
MAOI Monoamine oxidase inhibitor
MDD Major depressive disorder
OCD Obsessive-compulsive disorder
OH Orthostatic hypotension
PTSD Posttraumatic stress disorder
SGA Second-generation antipsychotic
SNRI Serotonin-norepinephrine reuptake inhibitor
SSRI Selective serotonin reuptake inhibitor
TCA Tricyclic antidepressant

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 during 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 4.5 kg (10 lb) in the past month. She is worried about her job and does not feel that 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 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, type 2 diabetes with newly diagnosed neuropathy, obesity, and coronary artery disease. She currently takes 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 with citalopram. She wants to change antidepressants. Which would be most beneficial?
   A. Bupropion.
   B. Duloxetine.
   C. Nortriptyline.
   D. Sertraline.

3. L.J. is a 45-year-old man who presents with agitation and diaphoresis and an oral temperature of 38.5°C (101.3°F). His right eyelid began twitching about an hour ago, and he cannot get it to stop. He developed cold symptoms 2 days ago and began taking dextromethorphan and pseudoephedrine. His 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 most likely 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 type 1 bipolar disorder, for which he takes lithium 300 mg twice daily. He has been adherent to treatment. His lithium serum concentration, taken
yesterday before his morning lithium dose, 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. For 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 (height 61 inches, weight 74.8 kg [165 lb], up from 68 kg [150 lb] 2 months ago) with a history of type I bipolar disorder. She has taken lithium 450 mg twice daily for the past 6 months. 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 (Na) 138 mEq/L, potassium (K) 4.7 mEq/L, serum creatinine (SCr) 0.9 mg/dL, glucose 124 mg/dL, and thyroid-stimulating hormone (TSH) 24 U/mL. Additional medications include olanzapine 10 mg at bedtime (for 1 year), ethinyl estradiol/drospirenone (Yasmin) daily, and a multivitamin. Which most likely accounts for the objective findings?
A. Hypothyroidism.
B. Lithium concentration.
C. Olanzapine.
D. Ethinyl estradiol/drospirenone.

6. I.T. is a 43-year-old woman with rapid-cycling bipolar disorder, hypertension, obesity, and asthma. She recently changed from lithium to divalproex sodium 500 mg daily. She also takes lamotrigine 150 mg twice daily, aripiprazole 30 mg daily, ramipril 10 mg daily, albuterol hydrofluoroalkane (HFA) 2 puffs every 6 hours, and fluticasone/salmeterol dry powder inhaler 250/50 twice daily. She started a prednisone taper 3 days ago for an asthma exacerbation. Today, she presents with right-sided abdominal pain with rebound tenderness, nausea, and vomiting. Laboratory test results include Na 141 mEq/L, K 3.3 mEq/L, chloride 95 mEq/L, carbon dioxide 26 mmol/L, SCr 1.0 mg/dL, glucose 72 mg/dL, total 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 most likely responsible for her 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 and alcohol use disorder. He was recently changed to aripiprazole from haloperidol because of gynecomastia and impotence. Today, he is pacing your office and seems anxious and agitated. He has not been sleeping well and feels uncomfortable in his skin. Which medication would be most appropriate to help relieve N.B.’s 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. During the past year, she has developed involuntary chewing motions and abnormal blinking, which have begun interfering with her ability to eat. She currently takes 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 change antipsychotics. She did not respond adequately to olanzapine or perphenazine. Which would most improve 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 given diagnoses of type 2 diabetes and dyslipidemia. Her body mass index (BMI) is 32 kg/m². Her father died of a myocardial infarction at age 42. She has been treated with risperidone but
developed galactorrhea. Concomitant medications include atorvastatin, metformin, and liraglutide. Which antipsychotic would be best?
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. A myocardial infarction has been ruled out. She has been given a diagnosis of panic disorder. Which medication regimen would most rapidly 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 (GAD). Concomitant medical conditions include a history of breast cancer, dyslipidemia, osteoarthritis, vasomotor 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 best?
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 has struggled with keeping a consistent bedtime for the past few months. She has no identifiable contributing factors. Concomitant medical conditions include hypertension, arthritis, and mild cognitive impairment. She has tried diphenhydramine but states that it helped for only a few nights and “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 successfully been 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 medications, nor does he abuse other substances. Which treatment regimen is most appropriate?
A. Initiate supervised buprenorphine/naloxone.  
B. Change to buprenorphine × 2 days; then take buprenorphine/naloxone.  
C. Change to naltrexone.  
D. Taper to methadone 30 mg; then change 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 several times to quit without success. He has recently reconciled with his estranged son and wants to be sober so that he can be 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 (PT) 0.9 seconds, platelet count 370,000/mm³, and creatinine clearance (CrCl) 40 mL/minute/1.73 m².

After detoxification, which maintenance treatment is most appropriate?
A. Acamprosate 333 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 a myocardial infarction. He has a 25 pack-year history of smoking cigarettes and smokes 1½ packs/day. He has tried twice unsuccessfully to quit. 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 about 6 months ago using the
2-mg strength of nicotine gum. To save money, he chewed 7 pieces daily. He currently has symptoms of depressed mood and anhedonia. Which regimen would be best?
A. Bupropion SR 150 mg twice daily.
B. Nicotine 4 mg gum.
C. Nicotine patch 21 mg/day.
D. Varenicline 0.5 mg once daily.
BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient-Centered Pharmacotherapy
   a. Task 1: 1-8, 10-14
   b. Task 3: 2 and 4
   d. Task 4: 1-7

2. Domain 3: System-Based Standards and Population-Based Pharmacotherapy
   a. Task 3: 1,4
Questions 1–4 pertain to the following case.
A 25-year-old man recently received a diagnosis of schizophrenia. 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 oculogyric crisis. The patient refused a rechallenge with haloperidol. Until now, he has not taken medications because he felt that he could control his symptoms on his own with vitamins and energy drinks, though he has difficulty remembering to take these.

1. Which is most appropriate for this patient’s symptoms at this time?
   A. Benztrapine.
   B. Haloperidol.
   C. Propranolol.
   D. Quetiapine.

2. The patient is initiated on risperidone. Which is the best rationale for this selection?
   A. Risperidone has minimal risk of causing extrapyramidal symptoms (EPS).
   B. Risperidone is available in a long-acting injection to increase adherence.
   C. Risperidone is effective for decreasing this patient’s negative symptoms.
   D. Risperidone can be dosed once daily after titration to target dose.

3. Which is the best example of an adverse effect of risperidone that would be of concern when initiated in this patient?
   A. Sedation.
   B. Anticholinergic effects.
   C. EPS.
   D. Corrected QT (QTc) prolongation.

4. One year later, your patient no longer responds to risperidone, and you decide to change his medication. He is only interested in oral medications. Given his history, which agent is most appropriate at this time?
   A. Clozapine.
   B. Fluphenazine.
   C. Olanzapine.
   D. Quetiapine.

I. SCHIZOPHRENIA

A. Characteristics
   1. Schizophrenia is a thought disorder involving psychosis and a complex mix of symptoms. The Diagnostic and Statistical Manual for Mental Disorders (DSM-5) identifies five symptoms for diagnosis. At least two of the following symptoms must be present for at least 1 month, and at least one of the symptoms should be delusions, hallucinations, or disorganized speech.
      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. Disorganized speech: This manifests as frequent “derailment” of speech or incoherence. “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.

d. Disorganized or catatonic behavior

e. Negative symptoms (see Table 1)

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 1.

Table 1. Categories of Schizophrenia-Associated Symptoms

<table>
<thead>
<tr>
<th>Positive (presence of something that should not be there)</th>
<th>Negative (absence of something that should be present)</th>
<th>Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional and Atypical Antipsychotics Effective</td>
<td>Atypical Antipsychotics May or May Not Be More Effective</td>
<td>No Current Medications Effectively Treat This</td>
</tr>
<tr>
<td>Hallucinations(^a,b)</td>
<td>Blunted or flat affect(^a,b)</td>
<td>Poor executive function</td>
</tr>
<tr>
<td>Delusions(^a,b)</td>
<td>Social withdrawal (passive-apathetic)(^a,b)</td>
<td>Impaired attention</td>
</tr>
<tr>
<td>Paranoia or suspiciousness(^a,b)</td>
<td>Lack of personal hygiene(^a)</td>
<td>Impaired working memory (does not learn from mistakes)</td>
</tr>
<tr>
<td>Conceptual disorganization(^a,b,c)</td>
<td>Prolonged time to respond(^a,b)</td>
<td></td>
</tr>
<tr>
<td>Hostility(^b)</td>
<td>Poor rapport(^b)</td>
<td></td>
</tr>
<tr>
<td>Grandiosity(^b)</td>
<td>Poor abstract thinking(^b)</td>
<td></td>
</tr>
<tr>
<td>Excitement(^b)</td>
<td>Poverty of speech (lack of spontaneity and flow of conversation)(^b)</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 Symptom Rating Scale (PSRS) and the Brief Negative Symptom Scale (BNSS).

\(^b\)These symptoms are used to score the positive and negative portions of the Positive and Negative Syndrome 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, circumstantiality, sudden topic shifts, incoherence, derailment, blocking, neologisms, clanging, word salad, and other speech disorders.
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 prevalence is around 1.1% and is equal between the sexes.
2. Most patients fluctuate between acute episodes and remission. Periods between episodes may include residual symptoms.
3. The lifetime course of schizophrenia has four phases: 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. This phase 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 remission without symptoms is 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. In some areas of the brain, dopamine overactivity appears to result in some symptoms, whereas in others, underactivity may occur.
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 Syndrome 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 Symptom Rating Scale (PSRS) and the Brief Negative Symptom Scale (BNSS) 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 BNSS 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 the BNSS allow rapid clinical assessment.
E. Antipsychotics (Table 2)
   1. First-line agents for treating schizophrenia
   2. Two classes
      a. First-generation antipsychotics (FGAs; also called typical or conventional antipsychotics): These include all the older antipsychotics, including the phenothiazines. Chlorpromazine was the first to be used clinically.
      b. Second-generation antipsychotics (SGAs; also called atypical antipsychotics): These include the newer agents, beginning with clozapine. The adverse effect profile of these agents is more heterogeneous and differs from that of FGAs.
   3. All antipsychotics carry a black box warning against use in older adults with dementia. FGAs may have a higher mortality rate than SGAs when used in older adults with dementia.

Table 2. Antipsychotic Agents for Schizophrenia by Chemical Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Degree of EPSa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected first-generation antipsychotics (FGAs; typical or conventional)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Chlorpromazine</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>Fluphenazine</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Mesoridazine</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Perphenazine</td>
<td>+2/+3</td>
</tr>
<tr>
<td></td>
<td>Thioridazine</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Trifluoperazine</td>
<td>+3</td>
</tr>
<tr>
<td>Butyrophenone</td>
<td>Haloperidol</td>
<td>+3</td>
</tr>
<tr>
<td>Others</td>
<td>Loxapine</td>
<td>+2/+3</td>
</tr>
<tr>
<td></td>
<td>Thiothixene</td>
<td>+3</td>
</tr>
<tr>
<td>Second-generation antipsychotics (SGAs; atypical)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Asenapine</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Brexpiprazole</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Cariprazine</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Iloperidone</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Lurasidone</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Paliperidone</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>0/+1</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>0/+1</td>
</tr>
</tbody>
</table>

a0 = none; +1 = low; +2 = moderate; +3 = high.
EPS = extrapyramidal symptoms.

4. Many antipsychotics are metabolized by the cytochrome P450 (CYP) system (Table 3). The presence of a CYP inducer or inhibitor may require antipsychotic dose adjustment. For example, tobacco dependence, particularly smoking, is common in patients with schizophrenia. A patient taking a CYP1A2 substrate antipsychotic who undergoes smoking cessation may require a reduced antipsychotic dose. This is particularly true of clozapine and olanzapine. Many SGAs metabolized by 2D6 and/or 3A4 carry dose adjustment recommendations.
Table 3. Selected Antipsychotics and the CYP System

<table>
<thead>
<tr>
<th></th>
<th>1A2</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>Asenapine</td>
<td>Aripiprazole</td>
<td>Aripiprazole</td>
</tr>
<tr>
<td></td>
<td>Clozapine*</td>
<td>Brexpiprazole*</td>
<td>Brexpiprazole*</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>Iloperidone*</td>
<td>Cariprazine*</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td>Perphenazine</td>
<td>Haloperidol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risperidone</td>
<td>Iloperidone*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lurasidone*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quetiapine*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ziprasidone</td>
</tr>
</tbody>
</table>

| Inducer  | Smoking         | Chlorpromazine  | |
| Inhibitor|                 | Fluphenazine    | |

*\*Dose adjustment required when used concomitantly with an inhibitor or inducer of that specific CYP enzyme.

5. QTc prolongation: Electrocardiographic (ECG) changes occur with antipsychotics. QTc prolongation can predispose the patient to ventricular arrhythmias, including torsades de pointes syndrome. The risk appears highest with chlorpromazine, haloperidol, and thioridazine. Among the SGAs, clozapine, ziprasidone, and iloperidone appear to have the highest risk, though the other agents may cause ECG changes to a lesser extent or only when combined with other agents that prolong the QTc interval. 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.

6. Venous thromboembolism (VTE): Three case-control studies and a retrospective study suggest an increased risk of VTE in patients taking antipsychotics. The risk may be higher in older adults and women. The risk appears greatest within the first 3 months of therapy.

F. FGAs for Schizophrenia (Table 2)

1. These agents can be categorized according to chemical class (Table 2) or potency as antagonists at the dopamine D₂ receptors (Table 4).

2. Potency at the D₂ receptors can be split into low and high. FGAs can be interconverted using dose equivalents.
   a. Low potency: Concomitant anticholinergic, antihistaminic, and α-adrenergic blocking properties are also present.
   b. High potency: Less potency at the other receptors; dopamine-related adverse effects, including EPS and hyperprolactinemia, tend to be the main adverse effect and is more prevalent than with low-potency agents
   c. Adverse effect profiles also differ by potency (Table 4).
Table 4. Selected FGAs for Schizophrenia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Equivalent (mg)</th>
<th>Potency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Anticholinergic&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Sedation&lt;sup&gt;b&lt;/sup&gt;</th>
<th>↓ BP&lt;sup&gt;b&lt;/sup&gt;</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>Fluphenazine</td>
<td>2</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>
<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>Perphenazine</td>
<td>10</td>
<td>Int.</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>Int.</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>Thiothixene</td>
<td>3–5</td>
<td>High</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>High</td>
</tr>
</tbody>
</table>

<sup>a</sup>Potency = D<sub>2</sub> receptor affinity

<sup>b</sup>Scale 1–5 = low to high.

BP = blood pressure; FGA = first-generation antipsychotic; Int. = intermediate.

3. Adverse effect profiles are relatively uniform for agents with similar dopamine potency.
   a. Sedation: More likely with low-potency agents. Sedation is usually worse initially and then tolerated better with time. Sedation tends to be dose related.
   b. Anticholinergic effects: Dry mouth, constipation, blurred vision, and urinary hesitancy can occur.
   c. Orthostatic hypotension (OH): Low-potency agents block the α-adrenergic receptor, which can cause OH.
   d. EPS: Four main manifestations:
      i. 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.
      ii. Dystonia: These episodes are often acute. The risk is greatest in young men and with high doses of parenteral antipsychotics. Examples include torticollis, laryngospasm, and oculogyric crisis. This is also treated with anticholinergics.
      iii. Akathisia: This is a somatic restlessness and the inability to stay still or calm. Reducing the antipsychotic dose and changing to an agent with a lower incidence of akathisia are the best options, but these are not always feasible. Akathisia responds poorly to anticholinergics. Lipophilic (fat soluble) β-blockers such as propranolol and nadolol have been used, but data analyses for efficacy are inconclusive. Benzodiazepines may reduce symptoms.
      iv. Tardive dyskinesia: Characterized by abnormal involuntary movements that occur with long-term antipsychotic therapy. Tardive dyskinesia usually involves the orofacial muscles and is often insidious. If caught early, it can be reversible. With continued drug exposure, particularly at high doses, tardive dyskinesia is often irreversible. Risks are likely related to total cumulative dose. Those taking high antipsychotic doses, those older than 54 years, women, and those with mood disorders are also at an increased risk. Symptoms may decrease with lowering the antipsychotic dose (after an initial symptom increase). However, this dose reduction must be weighed against worsening symptoms of schizophrenia. Changing to an agent that is associated with less tardive dyskinesia is also an option. The risk is higher with FGAs than with SGAs. Clozapine has not been associated with tardive dyskinesia, and changing to this drug may be appropriate for patients with moderate to severe symptoms. The other atypical antipsychotics also appear to have a low potential to cause tardive dyskinesia.
e. Valbenazine (Ingrezza) was U.S. Food and Drug Administration (FDA) approved on April 11, 2017, as the first drug to carry an indication for tardive dyskinesia. The exact mechanism of action is unknown, but valbenazine reversibly and selectively inhibits the vesicular monoamine transporter 2 (VMAT2). Valbenazine thus regulates the packaging of dopamine and other monoamines in the neuronal cytoplasm into vesicles for storage and release into synapses, decreasing the amount of dopamine released, which in turn results in fewer postsynaptic dopamine receptors and less dyskinetic movement. It is dosed once daily, and the dose must be adjusted for strong 3A4 and 2D6 inhibitors. Adverse effects include sleepiness, depression, and QT prolongation.

f. Anticholinergic agents should not be given to treat tardive dyskinesia and may in fact worsen the symptoms. Patients should be monitored regularly using the AIMS (Abnormal Involuntary Movement Scale).

g. Neuroleptic malignant syndrome: Occurs with all agents but appears more common with high-potency FGAs. It is manifested by agitation, confusion, changing levels of consciousness, muscle rigidity, fever, tachycardia, autonomic instability, and diaphoresis. The 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.

h. Endocrine effects: Breast enlargement, galactorrhea, sexual dysfunction, and menstrual changes can occur because of hyperprolactinemia caused by antipsychotics, particularly FGAs. Prolactin secretion is blocked by dopamine. Dopamine blockers can increase prolactin concentrations (hyperprolactinemia).

i. Weight gain: 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.

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

4. Therapy initiation: Most patients have symptom relief within the first few days with the recommended therapeutic doses. 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 (including acute dystonias) 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.

5. Route of administration: Oral therapy is most common; however, parenteral drugs can be used acutely if patients do not adhere to therapy, are agitated and will not take oral medications, or are a danger to themselves and/or others. Haloperidol can be given intramuscularly. Intravenous haloperidol has been linked to cardiac toxicity, including torsades de pointes, and is not recommended. 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 benefit and tolerability to oral therapy and have trouble adhering. Both haloperidol and fluphenazine decanoate may require “bridging” with oral therapy when treatment is initiated.

6. Therapy duration: The chronicity of schizophrenia usually results in lifelong antipsychotic treatment. Benefits of a particular medication must be weighed against long-term adverse effects (e.g., tardive dyskinesia) when selecting a specific antipsychotic. Relapse rates are more than 50% 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. Long-term therapy should include monitoring for metabolic complications such as diabetes, weight gain, and lipid abnormalities.
G. SGAs 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:
   a. The risk of EPS is lower than with typical antipsychotics at usual clinical doses,
   b. The risk of tardive dyskinesia is reduced, and
   c. 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. This may also be related to SGA efficacy in mood disorders.

2. Many clinicians see SGAs as first-line agents, likely because of the decreased risk of tardive dyskinesia. SGAs (particularly clozapine and olanzapine) have been associated with new-onset diabetes mellitus and metabolic syndrome. All patients prescribed SGAs should be monitored for weight, blood pressure, fasting glucose, lipids, and waist circumference at baseline and periodically thereafter.

3. Agents
   a. Clozapine (Clozaril): The first “atypical” antipsychotic. It is indicated only for treatment-resistant schizophrenia (defined as lack of response to two or more adequate trials of antipsychotics, including at least one FGA and one SGA). Lack of response usually refers to positive symptoms, although lack of response may include negative symptoms. Clozapine is the only antipsychotic indicated for reducing suicidal thinking in patients with schizophrenia or schizoaffective disorder. Clozapine is not associated with EPS or tardive dyskinesia, and it may be more effective at reducing negative symptoms than FGAs.
      i. Several black box warnings limit its use.
         (a) Severe neutropenia (agranulocytosis): This is the most limiting adverse effect. It can lead to a dramatic drop in neutrophils, which increases the risk of serious or fatal infections. It is defined as an absolute neutrophil count (ANC) less than 500 cells/mm$^3$. The incidence is about 0.9% and is highest during the first 4–6 months of therapy. Previously, both the white blood cell count and the ANC were used to monitor safety. As of 2015, only the ANC is used, and lower values are allowed for therapy. Allowances are also made for patients who have benign ethnic neutropenia (BEN; included in Table 5). Because of the severity of the neutropenia, all patients must be registered under a centrally managed Risk Evaluation and Mitigation Strategies (REMS) program (www.clozapinerems.com), which consolidates the six previous individual programs. Prescribers and pharmacies must also be registered. Laboratory work must be submitted to the national registry before clozapine can be dispensed. Details of hematologic monitoring are presented in Table 5.

Table 5. Hematologic Monitoring for Clozapine

<table>
<thead>
<tr>
<th>ANC Concentration</th>
<th>Clozapine Treatment Recommendations</th>
<th>ANC Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range for a new patient:</td>
<td>Initiate treatment</td>
<td>Weekly from initiation to 6 mo</td>
</tr>
<tr>
<td>General population (&gt; 1500 cells/mm$^3$)</td>
<td>If treatment interrupted:</td>
<td>Every 2 wk from 6 to 12 mo</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 days, continue monitoring as before</td>
<td>Monthly after 12 mo</td>
</tr>
<tr>
<td></td>
<td>≥ 30 days, monitor as if new patient</td>
<td></td>
</tr>
<tr>
<td>BEN population</td>
<td>Obtain at least two baseline ANC concentrations before initiating treatment</td>
<td></td>
</tr>
<tr>
<td>ANC Concentration</td>
<td>Clozapine Treatment Recommendations</td>
<td>ANC Monitoring</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Mild neutropenia  (1000–1499 cells/mm³)¹</td>
<td><strong>GENERAL POPULATION</strong>&lt;br&gt;Continue treatment</td>
<td><strong>GENERAL POPULATION</strong>&lt;br&gt;Three times weekly until ANC ≥ 1500 cells/mm³&lt;br&gt;Once ANC ≥ 1500 cells/mm³, return to patient’s last “normal-range” ANC monitoring interval²</td>
</tr>
<tr>
<td></td>
<td><strong>BEN POPULATION</strong>&lt;br&gt;Mild neutropenia is normal range for BEN population, continue treatment&lt;br&gt;Obtain at least two baseline ANC concentrations before initiating treatment&lt;br&gt;If treatment interrupted:&lt;br&gt;&lt; 30 days, continue monitoring as before&lt;br&gt;≥ 30 days, monitor as if new patient&lt;br&gt;Discontinuation for reasons other than neutropenia</td>
<td><strong>BEN POPULATION</strong>&lt;br&gt;Weekly from initiation to 6 mo&lt;br&gt;Every 2 wk from 6 to 12 mo&lt;br&gt;Monthly after 12 mo</td>
</tr>
<tr>
<td>Moderate neutropenia (500–999 cells/mm³)³</td>
<td><strong>GENERAL POPULATION</strong>&lt;br&gt;Recommend hematology consult&lt;br&gt;Interrupt treatment for suspected clozapine-induced neutropenia&lt;br&gt;Resume treatment once ANC &gt; 1000 cells/mm³</td>
<td><strong>GENERAL POPULATION</strong>&lt;br&gt;Daily until ANC ≥ 1000 cells/mm³; then&lt;br&gt;Three times weekly until ANC ≥ 1500 cells/mm³&lt;br&gt;Once ANC ≥ 1500 cells/mm³, check ANC weekly for 4 wk; then return to patient’s last “normal-range” ANC monitoring interval²</td>
</tr>
<tr>
<td></td>
<td><strong>BEN POPULATION</strong>&lt;br&gt;Recommend hematology consult&lt;br&gt;Continue treatment</td>
<td><strong>BEN POPULATION</strong>&lt;br&gt;Three times weekly until ANC ≥ 1000 cells/mm³ or ≥ patient’s known baseline&lt;br&gt;Once ANC ≥ 1000 cells/mm³ or a patient’s known baseline, check ANC weekly for 4 wk; then return to patient’s last “normal BEN range”³</td>
</tr>
<tr>
<td>Severe neutropenia (&lt; 500 cells/mm³)⁴</td>
<td><strong>GENERAL POPULATION</strong>&lt;br&gt;Recommend hematology consult&lt;br&gt;Interrupt treatment for suspected clozapine-induced neutropenia&lt;br&gt;Do not rechallenge unless prescriber determines that benefits outweigh risks</td>
<td><strong>GENERAL POPULATION</strong>&lt;br&gt;Daily until ANC ≥ 1000 cells/mm³&lt;br&gt;Three times weekly until ANC ≥ 1500 cells/mm³&lt;br&gt;If patient rechallenged, resume treatment as a new patient under “normal-range” monitoring once ANC ≥ 1500 cells/mm³</td>
</tr>
<tr>
<td></td>
<td><strong>BEN POPULATION</strong>&lt;br&gt;Recommend hematology consult&lt;br&gt;Interrupt treatment for suspected clozapine-induced neutropenia&lt;br&gt;Do not rechallenge unless prescriber determines that benefits outweigh risks</td>
<td><strong>BEN POPULATION</strong>&lt;br&gt;Daily until ANC ≥ 500 cells/mm³&lt;br&gt;Three times weekly until ANC ≥ a patient’s established baseline&lt;br&gt;If patient rechallenged, resume treatment as a new patient under “normal-range” monitoring once ANC ≥ 1000/mm³ or at patient’s baseline</td>
</tr>
</tbody>
</table>

¹ Confirm all initial reports of ANC > 1500 cells/mm³ with a repeat ANC measurement within 24 hr.
² If clinically appropriate.
³ ANC = absolute neutrophil count; BEN = benign ethnic neutropenia.
b. OH, bradycardia, syncope, and cardiac arrest: Is dose related and at highest risk at initiation of therapy or with rapid dose titration. Must be initiated at 12.5 mg once or twice daily, titrated slowly, and given in divided doses.

c. Seizures: Risk is dose related and can be minimized by starting low and titrating slowly.

d. Myocarditis and cardiomyopathy

ii. Additional adverse effects: These include weight gain, sedation, hypersalivation, rapid heart rate, and fever. The presence of fever should alert the clinician to the possibility of infection and agranulocytosis. If the drug is discontinued for 48 hours or more, retitration is required to avoid seizures or cardiac adverse effects.


c. 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.

d. Brexpiprazole (Rexulti): Approved for the treatment of schizophrenia and the adjunctive treatment of major depressive disorder (MDD). The most common dose-dependent adverse effects are akathisia, weight gain, and somnolence. Clinically significant weight gain (greater than 7%) occurs in 8%–12% of patients. It can also cause hyperglycemia and dyslipidemia. Must be adjusted for renal function.

e. Cariprazine (Vraylar): Approved for the treatment of schizophrenia and manic or mixed episodes associated with type I bipolar disorder. It is not recommended for patients with a CrCl less than 30 mL/minute/1.73 m². It is associated with dose-related OH, particularly at initiation and with dose increases. Limited studies suggest a low rate of weight gain over 6 weeks (1%–8% incidence, with 8% of those gaining more than 7%). Additional adverse drug reactions include gastrointestinal (GI) symptoms, somnolence, dizziness, parkinsonism (13%–21%), and seizures. Leukopenia and neutropenia have occurred, but there are no current recommendations to monitor.

f. 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.

g. Lurasidone (Latuda) has a low risk of metabolic and cardiac effects. Dose-related EPS may occur. It should be taken with at least 350 kcal of 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.

h. Olanzapine (Zyprexa): This drug is structurally similar to clozapine and has a similar pharmacologic profile. Unlike clozapine, however, it has not been associated with agranulocytosis. In one study, negative symptoms responded better than with haloperidol. Together with clozapine, olanzapine carries the highest risk of diabetes. For this reason, the PORT (Patient Outcomes Research Team) guidelines do not consider it a first-line treatment. It is also available as a depot injection (Relprevv). Because it has been associated with extreme sedation and delirium after administration, it is part of a REMS program (called the Zyprexa Relprevv Patient Care Program). Prescribers must undergo training, and it can only be administered within an approved institution where the patient has supervision postdose.
i. Paliperidone (Invega) is the major active metabolite of risperidone. Its pharmacologic profile is similar to that of the parent drug (see the text that follows). Paliperidone palmitate is also available as a monthly depot injection (Invega Sustenna).

j. Quetiapine (Seroquel): In addition to antagonism at the D₂ and serotonin-2 receptors, it has a high affinity for histamine-1 receptors. For this reason, it has a high incidence of somnolence and weight gain. May also cause OH. Unlike other antipsychotics, quetiapine offers a low incidence of EPS. For this reason, it is often used for psychosis associated with Parkinson disease, despite lack of strong evidence for efficacy.

k. Risperidone (Risperdal): This drug is a potent dopamine D₂ 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, OH, 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.

l. Ziprasidone (Geodon): Has a low incidence of metabolic syndrome, but can prolong the QTc interval. Use caution if combining it with other drugs (e.g., tricyclic antidepressants [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. It carries a warning for drug reaction with eosinophilia and systemic symptoms (DRESS), which can be fatal. It consists of three or more cutaneous reactions (including rash or exfoliative dermatitis), eosinophilia, fever, and lymphadenopathy and one or more of the following systemic complications: hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.

4. Table 6 summarizes the adverse effects associated with SGAs.

Table 6. Adverse Effects of SGAs

<table>
<thead>
<tr>
<th>Drug (generic/brand)</th>
<th>Metabolic Syndrome</th>
<th>Cardiac (clinically significant)</th>
<th>Sedation</th>
<th>Miscellaneous Clinically Significant Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight Gain</td>
<td>Diabetes Mellitus</td>
<td>Dyslipidemia</td>
<td>OH: Tolerance builds over 2–3 mo</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>Little to none</td>
<td>Possible QTc prolongation, OH</td>
</tr>
<tr>
<td>Brexpiprazole (Rexulti)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>Cariprazine (Vraylar)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>OH</td>
</tr>
</tbody>
</table>
Table 6. Adverse Effects of SGAs (Cont’d)

<table>
<thead>
<tr>
<th>Drug (generic/brand)</th>
<th>Metabolic Syndrome</th>
<th>Cardiac (clinically significant)</th>
<th>Sedation</th>
<th>Miscellaneous Clinically Significant Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight Gain</td>
<td>Diabetes Mellitus</td>
<td>Dyslipidemia</td>
<td>OH, prolonged QTc prolongation, OH tachycardia</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>Highest</td>
<td>High</td>
<td>High</td>
<td>OH, prolonged QTc prolongation, OH 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>High</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>Low</td>
<td>Low</td>
<td>None</td>
<td>Possible QTc prolongation</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>

antichol = anticholinergic; OH = orthostatic hypotension.

H. Adjunctive Medications
1. Lamotrigine may be beneficial when added to clozapine in patients with partial response. Data do not support the use of other anticonvulsants, including valproate, carbamazepine, and topiramate.
2. Benzodiazepines: May be useful during the acute phase for agitation or anxiety but are less effective for psychotic symptoms. These drugs must also be used with caution in patients with schizophrenia because this population is at high risk of substance use disorder.

I. Comparisons of FGAs and SGAs: Early clinical trial evidence suggested SGAs were more effective at reducing negative symptoms and had better tolerability than FGAs. Data from several large trials (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study [CUtLASS]; Arch Gen Psychiatry 2006;63:1079-87) and the Clinical Antipsychotic Trials of Intervention Effectiveness study (CATIE, sponsored by the National Institute of Mental Health) have not shown these differences. Almost all treatment guidelines now suggest that SGAs are preferred to FGAs as first-line agents. Reasons include a low incidence of neurological adverse effects in general, and tardive dyskinesia in particular, with SGAs over FGAs. Because of their serotonin-binding activities, SGAs also have efficacy against affective components of associated conditions, particularly schizoaffective disorders.
**Patient Case**
*Questions 5–8 pertain to the following case:*

A.Z. is a 45-year-old woman with sleep apnea, hypertension, type 2 diabetes, and chronic pain. She is in the clinic today for an assessment of her depressive symptoms and a medication evaluation. She endorses sad mood, poor appetite (lost 6.8 kg [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 currently takes hydrochlorothiazide, metformin, hydrocodone/acetaminophen, and aspirin. Her current BMI is 20 kg/m², and her blood pressure today is 152/94 mm Hg. She reports adherence to her current medications.

5. Which selective serotonin reuptake inhibitor (SSRI) would most likely interact with her current medications?
   A. Citalopram.
   B. Fluvoxamine.
   C. Paroxetine.
   D. Sertraline.

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

7. 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. Change to a different SSRI.

8. 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 citalopram.
   C. Change to a different SSRI.
   D. Change to mirtazapine.
II. 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. MDD, otherwise called unipolar disorder. MDD is diagnosed when a patient has at least five of the following symptoms almost 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: Psychometric instruments used to identify depression and assess its severity. Common examples include:
   a. The Hamilton Rating Scale for Depression (HAM-D): Often used to show efficacy in clinical trials for FDA approval of antidepressants. A common clinical trial enrollment score is greater than 18 (moderate-severe depression). 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.
   b. The CGI (Clinical Global Impressions) scale is a clinician-rated scale that evaluates the severity and improvement of patients overall.
   c. The MADRS (Montgomery-Åsberg Depression Rating Scale) is another instrument that evaluates symptoms of depression.

3. Patient rating scales: Patient-completed rating instruments. Answers to the questions are used to identify and assess the level of depression.
   a. Patient Health Questionnaire-9 (PHQ-9) is based on the *DSM-5* diagnostic criteria for major depression. It is easily administered and assessed. For this reason, it is often used in the primary care setting. Patients can be screened with an abbreviated version (the PHQ-2). If they test positive, the PHQ-9 is administered. The PHQ-9 can also be used to monitor treatment response.
   b. Beck Depression Inventory
   c. Quick Inventory of Depressive Symptoms Self-Rated

4. Physical examination and laboratory tests: 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 [CNS] 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). Takes longer to achieve effective results with psychotherapy than with pharmacotherapy. Psychotherapy may have broader and longer-lasting effects than pharmacotherapy monotherapy. Psychotherapy is recommended as monotherapy for initial treatment in patients with mild to moderate MDD (CBT and interpersonal therapy have the best evidence). Psychotherapy combined with pharmacotherapy is recommended for moderate to severe depression. Combination is more effective than either intervention alone.

2. Pharmacotherapy: Antidepressant therapy may lead to a more rapid response than psychotherapy, but when 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. ECT was also 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 equally efficacious. First-line medications include 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: Physical symptoms (energy levels, sleep disturbances) improve before affective symptoms. Symptoms can respond as early as 2 weeks. 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.

3. Adequate trial: An adequate trial includes the correct drug for the patient and a therapeutic dose for an appropriate duration. A therapeutic trial lasts 4–8 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; PHQ-9 less than 5). Optimizing the dose or duration is important for achieving remission.

5. Efficacy of antidepressants according to rigorous clinical trials occurs in 60%–70% of patients, regardless of drug. Effectiveness, which is more reflective of clinical practice, is lower, about 50%–60%. The remission rate with one antidepressant trial is about 30%, as seen in the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.
6. Drug interactions (Table 7): Many antidepressants are metabolized or inhibited by CYP enzymes.

Table 7. Antidepressants and the CYP System

<table>
<thead>
<tr>
<th>Substrate</th>
<th>1A2</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>Citalopram</td>
<td>Amitriptyline</td>
<td>Citalopram</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Duloxetine</td>
<td>Escitalopram</td>
<td>Escitalopram</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Fluoxetine</td>
<td>Fluoxetine</td>
<td>Levomilnacipran</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>3A4</td>
<td>Imipramine</td>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Vilazodone</td>
<td>Venlafaxine</td>
<td>Nortriptyline</td>
<td>Trazodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vortioxetine</td>
<td>Trazodone</td>
<td>Venlafaxine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nortriptyline</td>
<td>Venlafaxine</td>
<td></td>
</tr>
</tbody>
</table>

**Inducer**
- St. John’s wort

**Inhibitor**
- Fluvoxamine
- Bupropion
- Desvenlafaxine
- Duloxetine
- Venlafaxine
- Sertraline

*Boldface type in table body indicates strong inhibitor.

Table 8. 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>

E. Tricyclic Antidepressants

1. TCAs are effective, but adverse effects have limited their use. Now that newer agents with more tolerable adverse effect profiles are available, TCAs are used less often. TCAs have several off-label uses such as treatment for pain syndromes, migraine prophylaxis, and anxiety disorders.

2. TCAs block serotonin and norepinephrine uptake. Tertiary amines such as amitriptyline and imipramine are more potent for serotonin uptake and are metabolized to active secondary amines. The corresponding secondary amines (nortriptyline and desipramine, respectively) are more selective for norepinephrine.

3. TCAs have α-adrenergic blockade, antihistaminic, and anticholinergic effects, leading to orthostasis, sedation, and anticholinergic symptoms, respectively. TCAs can cause sexual dysfunction.

4. TCAs can be cardiotoxic in overdose (Table 8). They cause seizures and torsades de pointes. An actively suicidal patient should not receive a TCA.
5. These drugs are not recommended in patients with cardiac disease or seizure disorders. Patients at risk of OH are at increased risk of falls if they take these agents, and appropriate caution should be taken.

6. TCA serum concentrations can confirm adherence or toxicity. However, this is an infrequent clinical 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 norepinephrine. There are two forms of this enzyme (MAO-A and MAO-B), and drugs can block one or both of them.

2. Nonselective MAOIs (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 changing 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) to avoid serotonin toxicity. 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 for 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; Table 9)

1. SSRIs selectively inhibit the reuptake of serotonin into the presynaptic neuron and desensitize the presynaptic serotonin autoreceptor, resulting in increased serotonin concentrations. 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. Two additional SSRIs, vortioxetine and vilazodone, have additional activity and are covered separately in the text that follows.

Table 9. SSRI Characteristics

<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 hr</td>
<td>21 hr</td>
<td>15 hr</td>
<td>32 hr</td>
<td>27–32 hr</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 (depression)</td>
<td>300</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

*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. Adverse effect profiles differ slightly, and patients may tolerate one SSRI 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 (serotonin-2A, serotonin-2C, serotonin-3, and serotonin-4) may be responsible for some of the unwanted adverse effects (e.g., insomnia, restlessness, GI complaints). Activation, agitation, anxiety, or panic may occur 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 and sertraline, whereas paroxetine and fluvoxamine are the most sedating. Citalopram and escitalopram have no appreciable sedating or activating effects. Sexual dysfunction is more common than reported in the prescribing information and may occur in 50% or more of patients receiving these agents. Some interventions to consider for SSRI-induced sexual dysfunction in both sexes include using the wait-and-see method, adding bupropion for the treatment of sexual dysfunction, and lowering the SSRI dose. Sildenafil may be beneficial for men. Data are less robust for women.

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). Serotonin syndrome 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 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 flu-like 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 SSRI can be reinitiated and the dose gradually reduced again. It is most common with paroxetine, which has the shortest half-life; is less common with sertraline; and even less likely with fluoxetine, which has the longest half-life.

7. In 2011, the FDA ordered changes to citalopram package labeling, limiting the daily dose to a maximum of 40 mg because of an increased 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 who have concomitant medications that may increase the QTc interval should not be treated with citalopram. The maximal recommended citalopram dose 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 listed in Table 9 are available in generic form. The low cost and better tolerability and safety of SSRIs warrant their use 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 at least as effective as citalopram 20 mg, 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 increased incidence of both vertebral and non-vertebral bone fractures. Hyponatremia is a potential adverse effect, particularly in older adults.

H. Serotonin-Norepinephrine Reuptake Inhibitors
1. Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran block the reuptake of norepinephrine 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 norepinephrine compared with desvenlafaxine and duloxetine. At doses less than 150 mg/day, venlafaxine is a serotonin reuptake inhibitor.
   a. Whether the dual action of venlafaxine makes it more effective than SSRIs is an area of continued research. Some patients (e.g., treatment nonresponders) appear to benefit either from agents that affect norepinephrine and serotonin or from combinations of drugs with that effect.
   b. 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 has uncontrolled hypertension. This is a dose-related phenomenon, as described earlier.

2. Levomilnacipran (Fetzima) is the more potent enantiomer of milnacipran, which is approved for the treatment of fibromyalgia but not depression. Levomilnacipran is only approved for the treatment of depression, but not 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 OH can occur. It is a more potent inhibitor of norepinephrine than venlafaxine or duloxetine (norepinephrine slightly preferred to serotonin).

3. All the SNRIs may produce serotonin syndrome. In overdose situations, both duloxetine and venlafaxine have been associated with higher rates of death than SSRIs. The risk of suicide completion with SNRIs is still lower than with TCAs.

4. 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.

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

6. Desvenlafaxine (Pristiq) is an active metabolite of venlafaxine. It has no significant benefits over the parent drug.

7. Both desvenlafaxine and levomilnacipran doses must be tapered 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 the maximum doses are 40 mg daily. The most commonly associated adverse effects are nausea and diarrhea. It may cause a lower incidence of sexual dysfunction. It should not be used in patients with a history of seizure disorder. The dose must be tapered when given with strong 3A4 inhibitors.

2. Vortioxetine (Trintellix) is an SSRI, 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 in patients with depression 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 OH 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, like trazodone, is a serotonin-2A antagonist, but it also blocks the reuptake of serotonin and norepinephrine. Some have called this class “serotonin antagonist reuptake inhibitors” (serotonin-2A antagonist/reuptake inhibitors). Unlike trazodone, it causes minimal effects on sexual function and is less likely to cause OH. 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.

5. Mirtazapine is an antagonist of presynaptic α₂-autoreceptors and heteroreceptors, which results in an increase in norepinephrine and serotonin in the synapse. In addition, the drug blocks serotonin-2A (resulting in minimal to no sexual dysfunction, anxiety, or sedation), serotonin-3 (no nausea or 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 norepinephrine 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 norepinephrine 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 more often 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 may also increase energy and can cause psychosis in susceptible individuals. 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. 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 three remaining symptoms of depression.
   b. Continuation: The goal of this phase is to keep the symptoms in remission 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, including 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 6–8 weeks. If there is no response at this point, the drug can be considered a failure. With partial response, the trial can be extended to 12 weeks.

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 is defined as failing to respond to two or more agents from different classes. 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 be educated about therapy and closely monitored for adverse effects. Although most of the adverse effects are not life threatening, they do affect 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, norepinephrine, and dopamine differentially. Researchers are actively looking at specific symptoms of depression to determine whether certain presentations or symptom clusters 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. Treatment-Resistant Depression (Augmentation Therapy)
1. SGAs (or atypical antipsychotics) are commonly used as adjuncts to antidepressant therapy. Almost all of them have been used, but only aripiprazole, brexpiprazole, and quetiapine extended release have received FDA approval for this indication. Olanzapine in combination with fluoxetine is also approved for treatment-resistant depression.
2. Ketamine infusions
3. Others: Lithium, liothyronine, modafinil, scopolamine, buspirone

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 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, and cognitive therapy. Strategies did not differ significantly, but slightly higher remission rates occurred with augmentation. Bupropion and buspirone augmentation worked similarly, and bupropion 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 treatment level. 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. Changing 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 review of the STAR*D findings, see Am J Psychiatry 2006;163:1905-17.
Patient Case

Questions 9–11 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. His wife found that he was withdrawing their life savings from the bank. He states that he is the perfect candidate for the presidency. He is hypervocal 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 currently takes no 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. He has also received a diagnosis of hepatitis C.

9. 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.

10. Which treatment-emergent adverse effects would be of most concern and would require immediate evaluation if J.L. were prescribed lithium?
    A. Hypothyroidism.
    B. Coarse tremor.
    C. Severe acne.
    D. Weight gain.

11. Three months later, J.L. has been stable on lithium 900 mg/day. However, during a clinic visit, J.L. is confused and slurring his words. His lithium serum concentration is 1.9 mEq/L. He has been taking lisinopril and atorvastatin again for his hypertension and dyslipidemia for 2 months. He takes zolpidem for sleep. He began running a week ago. He has been replacing fluids using an oral rehydrating solution (Gatorade) and taking ibuprofen as needed for pain. His other medications include lisinopril, atorvastatin, and zolpidem. Which most likely contributed to this patient’s current clinical situation?
    A. Gatorade.
    B. Ibuprofen.
    C. Lisinopril.
    D. Zolpidem.

III. 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 of 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 (I and II):
   a. Bipolar I: Chronic disorder marked by one or more manic or mixed episodes and major depressive episodes
   b. Bipolar 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 four 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 type I bipolar disorder. 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. Lithium also has anti-suicidal effects when used to treat 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 the 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 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, 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 to rule out toxicity. 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 postdose concentrations, so concentrations should be ordered 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, particularly during therapy initiation or after dose changes. Common adverse effects are listed in Table 10.
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 concentration and sodium/renal function should be obtained so that lithium concentrations can be accurately estimated.
Table 10. 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>GI (nausea, vomiting, diarrhea)</td>
<td>Reduce dose; try extended-release product, split doses</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 HCTZ will ↑ Li Cp; single bedtime dosing helps</td>
</tr>
<tr>
<td>Interstitial fibrosis, glomerulosclerosis</td>
<td>Keep dose at lowest effective concentration; avoid dehydration</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. Pregnancy: Lithium is teratogenic, particularly in the first trimester. Women of childbearing age should be counseled on its potential effects. Risks of discontinuing lithium therapy must be weighed against effects on the fetus when making decisions regarding lithium therapy during pregnancy.

11. Situations to consider during lithium therapy are listed in Table 11.

Table 11. 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></td>
<td>Thiazides</td>
<td>↑ Li Cp; avoid use to reduce toxicity</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>↑ Li Cp; avoid use to reduce toxicity</td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td>Little effect</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
<td>↑ Li Cp; avoid use to reduce toxicity</td>
</tr>
<tr>
<td></td>
<td>Theophylline</td>
<td>↓ Li Cp</td>
</tr>
<tr>
<td></td>
<td>ACEIs</td>
<td>↑ Li Cp; avoid use to reduce toxicity</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular blockers</td>
<td>Li prolongs action</td>
</tr>
<tr>
<td></td>
<td>Neuroleptics</td>
<td>Li may potentiate EPS</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine</td>
<td>↑ CNS toxicity</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></td>
<td>↑ Sensitivity to ADRs</td>
<td>Li toxicity</td>
</tr>
<tr>
<td>↓ Renal function</td>
<td>↓ GFR, ↑ creatinine and BUN</td>
<td>↑ Li Cp</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; ADR = adverse drug reaction; BUN = blood urea nitrogen; GFR = glomerular filtration rate; NSAID = nonsteroidal anti-inflammatory drug.
C. Anticonvulsants for Bipolar Disorder: These are also considered mood-stabilizing drugs that reduce manic and depressive episodes. See the Neurology chapter for additional drug-specific details.

1. Divalproex: 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 use disorder. Target serum concentrations are 50–125 mcg/mL. The serum concentration can be checked 3–5 days after initiation or after a change of dose. Serum concentration should be interpreted in connection with clinical response. 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 is uncommon (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: Effective for acute mania and maintenance therapy, particularly in patients with a history of head injury. Equetro is FDA approved 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 for the prevention of future depressive episodes of bipolar disorder. It is less effective than other mood stabilizers for the prevention of 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. Other anticonvulsants, including levetiracetam, oxcarbazepine, and topiramate, are used for bipolar disorder, but data regarding their efficacy are scarce. Data for gabapentin suggest it is ineffective.
D. Antipsychotics for Bipolar Disorder: Antipsychotics, particularly SGAs, 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, and irritation. They are often combined with a traditional mood stabilizer for severe symptoms. All SGAs have received FDA approval for use in acute mania or mixed episodes except for brexpiprazole, 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. Olanzapine is also approved for treatment of bipolar depression when combined with fluoxetine. Data for aripiprazole suggest it is ineffective for the treatment of bipolar depression.

3. Maintenance treatment: The long-acting injectable antipsychotic formulations Risperdal Consta and Abilify Maintena have been approved for use in bipolar maintenance as monotherapy. The CANMAT/ISBD guidelines also 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 International Society for Bipolar Disorders stopped short of recommending against any use of antidepressants. However, 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 Enhancement 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 switch to a manic phase (N Engl J Med 2007;356:1711-22).

2. Fluoxetine in combination with olanzapine is approved to treat depression associated with type I bipolar disorder.

G. Type II Bipolar Disorder: The depressive phase tends to be more debilitating. Patients are usually functional during hypomanic episodes. Treatment therefore focuses on the depressive phase. Lithium is a first-line agent, but it may not achieve remission as monotherapy and takes time to relieve symptoms. Quetiapine is preferred for acute symptom treatment. Lurasidone may also be used. Lamotrigine is a reasonable alternative for longer-term symptom control, but because of its slow titration schedule, it is not useful in the acute setting. Other mood stabilizers can be used but may not be as efficacious as for type I. Antidepressants are used more commonly but should be used with caution, and never as monotherapy. Olanzapine and fluoxetine may thus be an option.
**Patient Case**

*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 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.

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 AND RELATED DISORDERS (OCD, PTSD)**

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 two 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. 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.

5. **Specific phobias** are characterized by intense fear or anxiety induced by a specific object.

6. OCD, which used to be classified as an anxiety disorder, now has its own designation. 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).

7. PTSD, which also used to be classified as an anxiety disorder, has been moved to a category titled “Trauma- and Stressor-Related Disorders.” PTSD follows a traumatic event. It is characterized by increased arousal and avoidance of stimuli that approximate the original traumatic event.

**B. Pharmacotherapeutic Options for Anxiety and Related Disorders**

1. **Benzodiazepines**: These drugs have anxiolytic properties, and some have preventive efficacy for panic attacks. They are not effective for all anxiety disorders. Depending on the choice of agent, the onset can be very rapid, as outlined in the text that follows. 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 psychological 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 older adult patients.

   iii. Table 12 compares the half-lives and potencies of the five main/most commonly prescribed benzodiazepines in the treatment of anxiety disorders.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Half-life (hr)</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</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</td>
<td>10</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>10–18</td>
<td>1</td>
</tr>
</tbody>
</table>

*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. For this reason, it is generally recommended that treatment periods be restricted to 3–4 weeks, 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 use disorder or risk factors for substance use disorder, 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. TCAs have preventive efficacy for panic disorder and anxiolytic activity.

   **Important note:** About 25% of patients with anxiety disorders (particularly GAD and panic disorder) have a hyperstimulatory 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 anxiety disorders.

C. Recommended Therapy for Specific Anxiety and Related Disorders

1. GAD
   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 weeks, 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 use disorder); 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 be included with pharmacotherapy.
f. In treatment-refractory patients, augmentation with quetiapine, olanzapine, or risperidone can be tried.
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 adverse effects. For this reason, these patients should be initiated on low doses of antidepressants—as low as 25 mg of sertraline or 10 mg of paroxetine.
3. OCD
   a. Serotonergic agents are effective—SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) and clomipramine. Patients tend to require higher doses.
   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. PTSD
   a. Psychotherapy is considered the cornerstone of therapy. Effective methods incorporate CBT, including exposure therapy and trauma-based CBT.
   b. Medications are considered adjuncts to psychotherapy. They are preferred if psychotherapists are not readily available.
   c. SSRIs (fluoxetine, sertraline, and paroxetine) are considered first-line agents.
   d. Augment with other agents to treat specific symptoms (e.g., intermittent explosive behavior with β-blockers or mood stabilizers).
      i. Prazosin is used to treat PTSD-associated nightmares.
      ii. Anticonvulsants for aggression, anger, and depression (valproic acid, carbamazepine, lamotrigine, topiramate)
      iii. Atypical antipsychotics for psychotic symptoms (olanzapine, quetiapine, risperidone)
   e. Benzodiazepines are sometimes used acutely for sleep disturbances, but use should be very limited. Most data analyses indicate a lack of efficacy. Benzodiazepines have dissociative and disinhibiting properties and may worsen non-hyperarousal symptoms. Benzodiazepines may also interfere with the fear conditioning aspects of psychotherapy.
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 adjunctive therapy.
   d. Gabapentin and pregabalin are used as second- or third-line agents.
6. Specific phobias
   a. Not treated with medication
   b. Systematic desensitization and other behavioral approaches often effective
Patient Case
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 she can take any other medications. 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.

18. Which adverse effect of zolpidem carries the greatest potential for harm?
   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 shown in Table 13.

Table 13. 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 min</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. Older adult 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 one-half of those saying it is serious.
   b. More than 40% of those with insomnia self-medicate with over-the-counter medications (discussed in the text that follows) or other substances (e.g., alcohol).
   c. Insomnia can be classified according to symptom duration, as in Table 14.
**Table 14. Types of Insomnia**

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration (wk)</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 use disorder</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 syndrome; these are no longer recognized by the <em>DSM-5</em> 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 stated later in the text) 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 as follows:
   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 use disorder, 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; 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. Doxepin is a TCA.

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 CNS 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 falling asleep would probably 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. Table 15 compares the benzodiazepines available in the United States.

Table 15. Benzodiazepines for Insomnia

<table>
<thead>
<tr>
<th>Drug (trade)</th>
<th>Usual Dose (mg)</th>
<th>Half-Life (hr)</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 a history of substance use disorder 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 at 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. Incidence may be dose-dependent.
e. Be careful when using benzodiazepines in older adult patients because benzodiazepines 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 older adult 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 16. Non-benzodiazepines for Insomnia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life (hr)</th>
<th>Administration (minutes before sleep)</th>
<th>Indications</th>
<th>DEA 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>Doxepin: 15.3</td>
<td>30</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nordoxepin: 31</td>
<td></td>
<td></td>
<td>Not controlled</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>1–2.6</td>
<td>30</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Suvorexant (Belsomra)</td>
<td>12</td>
<td>30</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Zaleplon (Sonata)</td>
<td>1</td>
<td>Immediately</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Zolpidem (Ambien)</td>
<td>1.4–6.5 (see the text that follows)</td>
<td>Immediately</td>
<td>X (CR only)</td>
<td></td>
</tr>
</tbody>
</table>

6. Doxepin (Silenor) is a TCA 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 because of the long half-life of both doxepin and its active metabolite, nordoxepin.

7. Eszopiclone (Lunesta): This non-benzodiazepine is a GABA\textsubscript{A} agonist. Its half-life is 6 hours, so morning effects can 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 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- to 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 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 CYP1A2, but inducers and inhibitors of 2C9 and 3A4 can also affect it.

9. Suvorexant (Belsomra) is an orexin receptor antagonist. The neuropeptide orexin promotes wakefulness. By blocking the OX1R and 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 CYP3A4, and the dose must be decreased in patients taking concomitant 3A4 inhibitors. It is contraindicated in patients with narcolepsy.
10. Zaleplon: This is a non-benzodiazepine with a pharmacology similar to zolpidem (see below) and a very short half-life. For patients with sleep maintenance problems, it may 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.

11. Zolpidem: This non-benzodiazepine sedative-hypnotic modulates the GABA<sub>A</sub> receptor complex.
   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 depending on the dosing form. The sublingual spray has a shorter onset of action, but that of the sublingual tablet is comparable with both the IR and the 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 patients who have difficulty falling back to sleep as long as 4 hours or more remain.
   d. The FDA has reduced the dosing recommendations to limit next-day impairment. The dosing differs on the basis of the patient’s sex 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 complex behaviors 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 16 with food can delay onset of effects, thus prolonging the time to onset of sleep and increasing the risk of 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 older adult 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 Case

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 initiated. 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.

21. Before administering fluids with glucose, which agent is most important to administer?
   A. Folate.
   B. Multivitamin supplement.
   C. B₁₂.
   D. Thiamine.

22. Which medication is best for L.M.'s alcohol dependence?
   A. Acamprosate.
   B. Diazepam.
   C. Disulfiram.
   D. Naltrexone.

VI. SUBSTANCE USE DISORDERS

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 17 lists the stages of acute alcohol withdrawal.

Table 17. Stages of Acute Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Stage</th>
<th>Onset</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6–12 hr</td>
<td>Mild tremors, irritability, mild agitation, restlessness, tachycardia, nausea, sweating</td>
</tr>
<tr>
<td>2</td>
<td>12–24 hr</td>
<td>Marked tremors, hyperactivity, hyperalertness, increased startle response, pronounced tachycardia, insomnia, nightmares, illusions, hallucinations, alcohol cravings</td>
</tr>
<tr>
<td>3</td>
<td>12–48 hr</td>
<td>More severe symptoms than during stage 2; seizures may occur</td>
</tr>
<tr>
<td>4</td>
<td>3–5 days</td>
<td>Delirium tremens: Confusion, agitation, tremor, insomnia, tachycardia, sweating, hyperpyrexia</td>
</tr>
</tbody>
</table>

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 treatment level 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. Because of cross-tolerance, benzodiazepines can be used therapeutically to prevent and/or treat withdrawal symptoms. Several dosing regimens are used (Table 18).

i. Symptom-driven treatment using the Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar) is the most common method. The CIWA-Ar consists of seven items and has a range of 0–67. The higher the score, the more severe the symptoms. The patient’s CIWA-Ar score is determined every hour. Patients are typically treated if the score is greater than 8–10 (depending on protocol). This protocol is efficacious and results in lower total benzodiazepine use.

ii. Scheduled dosing: For severe alcohol withdrawal, fixed-dose benzodiazepine therapy is used for 2–3 days, regardless of symptoms, with supplementation according to the hourly CIWA-Ar score. The benzodiazepine can then be tapered 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 at a dose of 10–20 mg every 1–2 hours until the withdrawal symptoms 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. Chlordiazepoxide is considered the “classic” benzodiazepine for treating alcohol withdrawal because it was used first. It has no proven advantages over the other agents. Its long half-life may cause unnecessary sedation, particularly in patients with liver dysfunction. Conversely, patients with a high risk of withdrawal seizures or delirium tremens may need a long-acting benzodiazepine.

v. Lorazepam is preferred in most situations. Its shorter half-life allows for tighter control of dosing with minimal risk of oversedation.
Table 18. Benzodiazepines for Acute Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Drug</th>
<th>CIWA-Ar Dosing</th>
<th>Fixed-Dose Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam (Ativan)</td>
<td>2–4 mg PO/IV/IM</td>
<td>2 mg every 6 hr x 4; then 1 mg every 6 hr x 8</td>
<td>Preferred medication, particularly for liver disease; no active metabolites</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>10–20 mg PO/IV/IM</td>
<td>10 mg every 5 hr x 4; then 5 mg every 6 hr x 8</td>
<td>Decrease dose for liver disease</td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>50–100 mg PO/IV</td>
<td>50 mg every 6 hr x 4; then 25 mg every 6 hr x 8</td>
<td>Long acting; decrease dose for liver disease</td>
</tr>
</tbody>
</table>

*IM administration of diazepam is unreliable.

IM = intramuscular(ly); IV = intravenous(ly); PO = orally.

c. 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).
   v. 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).
   vi. Hallucinations: Benzodiazepine will usually manage hallucinations effectively; if not, give haloperidol; however, be cautious because haloperidol can lower the seizure threshold.
   vii. Seizures: Benzodiazepines 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 efficacy varies.

d. Other agents
   i. β-Blockers: These agents help with tremor, heart rate, 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 it 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 can 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. Most (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 attributable to overdose with opioid analgesics occurred, accounting for 72% of all deaths caused by overdoses with pharmaceuticals.

2. The potential for abuse led the Drug Enforcement Administration to reclassify products containing hydrocodone and acetaminophen from C-III to C-II.

3. Opioid withdrawal is not life threatening in the 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.

4. 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.

5. The use of buprenorphine came about as a result of the Drug Addiction 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. Several formulations are FDA approved for the treatment of opioid dependence: buprenorphine (available as sublingual tablets [Subutex]), buprenorphine/naloxone (available in 4:1 ratio dosing increments as sublingual tablets [Zubsolv], sublingual film [Suboxone], and buccal film [Bunavail]), and the buprenorphine implantable subdermal device (Probuphine).
   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 can precipitate withdrawal.
   c. Adding naloxone reduces abuse potential because naloxone is more rapidly inactivated after oral/sublingual absorption than parenteral administration. Thus, if the medication is used as intended (sublingually), the likelihood of withdrawal symptoms is low as opposed to dissolving and injecting it.
   d. Probuphine consists of four 1-inch flexible rods that are implanted under the skin in the arm. The rods release buprenorphine for up to 6 months, after which time they are removed. It is indicated for maintenance treatment of opioid dependence in patients who have had prolonged clinical stability on doses of a transmucosal buprenorphine product of no more than 8 mg/day of Subutex, Suboxone, or a generic equivalent.

6. Treatment with buprenorphine involves three phases: induction, stabilization, and maintenance. Buprenorphine/naloxone is preferred 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 (around 12–24 hours since the last dose of short-acting opioid). They must also be screened for other substance use disorder 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 buprenorphine is less likely to induce withdrawal.
b. Patients should 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 consider all psychosocial factors.

c. Induction phase: Find the minimum buprenorphine dose 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 if they 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 adverse 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 to 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.

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

C. Tobacco Dependence
1. Tobacco use is the main cause of preventable morbidity and mortality.
2. Tobacco use increases the risk of cardiovascular disease (including stroke), chronic obstructive pulmonary disease, and cancer (both lung and non-lung).
3. According to the 2012–2013 National Adult Tobacco Survey, 21.3% of Americans use a tobacco product every day or on most days, and 19.2% use some form of combustible tobacco product. Cigarettes are the most commonly used product. Rates of tobacco use have greatly declined over the past decade, and there are now 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 few as 3 minutes can make a difference. Patient counseling can help encourage patients who are unwilling to quit to reconsider quitting and act on it in the future.
5. As of January 2015, the Joint Commission requires 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. On average, seven attempts are necessary for a patient to quit successfully.
7. Willingness to quit should be assessed by 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 can help identify barriers to change and help the patient overcome them.
9. The five R’s can 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 non-nicotine) are available to help. They should be used with nonpharmacologic modalities to increase the success of quitting.
13. Nicotine replacement therapy: All forms are equally efficacious. Patients should be advised to stop smoking completely before initiating. Nicotine replacement therapy is available 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, if needed, to improve success. It is recommended to change the patch when awakening every day. Rotate sites.

   b. Gum: The gum should be chewed until a “peppery” or flavored taste develops; then the gum should be “parked” 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. Adverse 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 chewed or swallowed. The frequency of use and tapering are the same as for the gum. Adverse 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 about 20 minutes. Recommended treatment length is 3 months, with reduction in frequency during the past 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 adverse 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 or two doses should be used hourly, up to five doses. The 24-hour maximum is 40 doses. At least eight doses should be used at the start of therapy. Each bottle contains 100 doses. Recommended length of therapy is 3–6 months, with tapering. Risk of dependency is higher than with other forms of nicotine replacement. Inhaling, sniffing, and swallowing can increase the risk of nasal irritation and should thus be avoided when taking the spray. Nasal irritation can occur in up to 94% of patients. Although nasal irritation can resolve, many patients may have it as long as 8 weeks into therapy. Nasal spray is not recommended for 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. Nicotine replacement therapy has not been shown 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. Bupropion can also be combined with the nicotine patch, if needed.
15. **Varenicline**: A nicotine receptor partial agonist. Varenicline blocks the effects of nicotine from smoking. Varenicline should be started 1 week before the quit day, though patients can choose to quit smoking up to 35 days after starting varenicline. Varenicline should be continued for a total of 12 weeks. If the patient is successful at smoking cessation, varenicline 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. A recent meta-analysis and systematic review suggests that the risk of neuropsychiatric symptoms is not significantly different from placebo (BMJ 2015;350:h1109). A 2011 FDA advisory warned of a small increase in the risk of cardiovascular events, particularly in patients with preexisting cardiovascular disease. The benefits of smoking cessation must be weighed against the possible risk. Varenicline must be used with caution in patients with a CrCl less than 30 mL/minute/1.73 m². Combining varenicline with nicotine replacement therapy may increase adverse effects, though varenicline has been used in combination with the nicotine patch. Varenicline 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.

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Substance Use Disorders


ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: A**
Benztropine or another anticholinergic should be given to reverse the EPS symptoms (neck stiffness) (Answer A is correct). Haloperidol, an FGA, would worsen symptoms (Answer B is incorrect). Although the incidence of EPS is low with quetiapine, quetiapine would not help resolve this patient’s current symptoms (Answer D is incorrect). Propranolol is useful for akathisia but not for other types of EPS (Answer C is incorrect).

2. **Answer: B**
Risperidone has less risk of EPS than haloperidol/FGAs, but risperidone has the greatest risk among the SGAs (Answer A is incorrect). Like other SGAs, risperidone is effective for negative symptoms and can be dosed once daily after reaching the target dose. Because this patient has difficulty remembering to take a tablet daily (e.g., a vitamin), the best reason to use risperidone in this patient is that he can be converted to a long-acting injection formulation (Risperdal Consta) given twice a month (Answer B is correct; Answers C and D are incorrect).

3. **Answer: C**
Risperidone is more likely to cause EPS than other SGAs (Answer C is correct). Risperidone may cause sedation but not appreciably so (Answer A is incorrect). Anticholinergic effects are minimal with risperidone (Answer B is incorrect). Although all antipsychotics can potentially cause QTc prolongation, they rarely cause problems in patients without risk factors (Answer D is incorrect).

4. **Answer: D**
Quetiapine would be most appropriate, given the patient’s history of dystonia with haloperidol (Answer D is correct). Quetiapine carries a lower risk of causing EPS than FGAs such as fluphenazine (Answer B is incorrect). Clozapine and olanzapine have low risks of EPS as well, but clozapine is reserved for treatment-resistant cases (Answer A is incorrect). Olanzapine would not be preferred because of the significant metabolic risks it could cause in this young patient (Answer C is incorrect).

5. **Answer: C**
Paroxetine would have the most interaction with this patient’s current medications because of its interaction with hydrocodone by inhibiting the CYP2D6 isoenzyme (Answer C is correct). This would result in a lack of analgesic effects from the opiate. Fluvoxamine is a CYP1A2 inhibitor that does not interact with thiazides, metformin, or opiates (Answer B is incorrect). Citalopram would have no appreciable effects on any of this patient’s medications (Answer A is incorrect). The effect of sertraline, though it may compete with hydromorphone (metabolite of hydrocodone) through CYP3A4, is less than that of paroxetine (Answer D is incorrect).

6. **Answer: C**
Mirtazapine is appropriate because it can improve this patient’s insomnia and poor appetite (Answer C is correct). In addition, mirtazapine has no drug-drug interactions with the patient’s current medications. Bupropion, fluoxetine, and venlafaxine would worsen her insomnia (Answers A, B, and D are incorrect). At doses greater than 150 mg daily, venlafaxine would worsen hypertension (Answer D is incorrect), and bupropion decreases appetite (Answer A is incorrect).

7. **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 (Answer B is correct). The patient has taken citalopram for only 4 weeks, possibly at a subtherapeutic dose (Answer A is incorrect). Bupropion can be added later, after the patient has reached a maximal tolerated citalopram dose for 6–8 weeks (which is a therapeutic trial) (Answer C is incorrect). Changing SSRIs may also be an option after the maximal tolerated citalopram dose is reached (Answer D is incorrect).

8. **Answer: B**
The patient still needs an antidepressant, and discontinuing citalopram without an alternative agent at 6 months would be inappropriate (Answer A is incorrect). Bupropion can be added to treat the patient’s anorgasmia and may augment mood effects (Answer
B is correct). Changing to a different SSRI might produce the same adverse effect because the patient’s anorgasmia appears to be caused by serotonergic activity (Answer C is incorrect). Changing to mirtazapine would be inappropriate because the patient has had a therapeutic response and has been doing well for 6 months (Answer D is incorrect).

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

10. Answer: B
Coarse tremor may indicate lithium toxicity and will require an immediate evaluation of the patient’s lithium concentration (Answer B is correct). Lithium can cause hypothyroidism, severe acne, and weight gain, but these can usually be managed with lifestyle modifications or medications (Answers A, C, and D are incorrect).

11. Answer: B
This patient has lithium toxicity, as evidenced by the lithium concentration (1.9 mEq/L) and the accompanying symptoms of confusion and slurred words. Both lisinopril and ibuprofen can increase lithium concentrations. The patient has been taking lisinopril for 2 months; thus, the lithium concentration should be stabilized (Answer C is incorrect). Ibuprofen was started in the past week and thus is the most likely culprit (Answer B is correct). Zolpidem might increase sedation, but it should not result in the current symptoms (Answer D is incorrect). The sodium in the oral rehydration solution would be expected to decrease the lithium concentrations, not increase them (Answer A is incorrect).

12. Answer: A
Paroxetine should be continued at this time because the patient is successfully being treated for depression, and paroxetine is considered a first-line agent for PTSD (Answer A is correct). Sertraline also treats PTSD, but there is no reason to discontinue paroxetine (Answer B is incorrect). Adding adjunctive agents such as lorazepam and buspirone is not indicated because paroxetine was initiated only 3 weeks ago (Answers C and D are incorrect).

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

14. Answer: D
Buspirone is not a benzodiazepine and does not have much dependence potential (Answer D is correct). Buspirone does not relieve nightmares (Answer A is incorrect), and it is dosed three times daily (Answer C is incorrect). Buspirone also takes about 2 weeks for the onset of effect (Answer B is incorrect).

15. Answer: A
Clomipramine is the most serotonergic drug of the choices provided and is highly effective for OCD (Answer A is correct; Answers B–D are incorrect).

16. Answer: D
The patient takes levothyroxine at nighttime, which is probably contributing to her insomnia (Answer D is correct). Hydrochlorothiazide and ibuprofen are not significantly associated with causing insomnia (Answers B and C are incorrect). Citalopram might contribute to insomnia in certain patients, but this patient takes it in the morning, which decreases the risk (Answer A is incorrect).

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

18. **Answer: C**
Zolpidem and other sedative-hypnotics have been associated with abnormal behaviors such as eating, driving, having sex, and talking on the telephone while asleep (Answer C is correct). Zolpidem may cause orthostasis and disorientation but, when taken appropriately, does not cause significant problems (Answers A and B are incorrect). Zolpidem at high doses has been associated with seizures, but this patient has no history of drug abuse or of using high doses of medications (Answer D is incorrect).

19. **Answer: C**
The initial symptoms of alcohol withdrawal include hemodynamic instability such as increased heart rate and blood pressure (Answer C is correct). Alcohol craving, delirium tremens, and seizures generally occur after 12 hours of abstinence (Answers A, B, and D, respectively, are incorrect).

20. **Answer: D**
Lorazepam can be given intramuscularly and is appropriate because of the patient’s liver abnormalities (Answer D is correct). Lorazepam undergoes glucuronidation and does not rely on oxidative pathways for metabolism. Chlordiazepoxide and diazepam should be avoided in patients with liver disease (Answers A and C are incorrect). Clonazepam is generally not used for alcohol withdrawal and is not given intramuscularly (Answer B is incorrect).

21. **Answer: A**
Given the patient’s liver disease, acamprosate is most appropriate because it does not rely on hepatic metabolism (Answer A is correct). Disulfiram and naltrexone are not generally recommended in patients with liver disease (Answers C and D are incorrect). Diazepam is not used for alcohol dependence but is used during alcohol withdrawal (Answer B is incorrect).
1. **Answer: B**
An SSRI would be considered the first-line agent in this patient. Fluoxetine’s adverse effect profile most closely counteracts the patient’s symptoms. She also has anxiety, and fluoxetine could concomitantly relieve her symptoms of anxiety and allow her to stop taking benzodiazepine (Answer B is correct). Paroxetine can increase appetite and cause somnolence (Answer D is incorrect), as can mirtazapine (Answer C is incorrect). Although her suicidal ideation is intermittent and passive, desipramine can be fatal in an overdose situation (Answer A is incorrect).

2. **Answer: B**
Duloxetine is the best choice because it is also indicated for diabetic neuropathy (Answer B is correct). Although nortriptyline is effective for neuropathy, it is not a good choice in a patient with cardiovascular disease. Nortriptyline could also cause weight gain (Answer C is incorrect). Although bupropion is either weight neutral or can lead to some weight loss, data are not strong for use in neuropathy (Answer A is incorrect). Sertraline would be safe in this patient and could be used as an alternative to citalopram, but it is not effective for neuropathy (Answer D is incorrect).

3. **Answer: D**
This patient has 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 (Answer D is correct). None of the other choices is a combination of serotonergic agents, nor do they interact in a fashion that would increase serotonergic activity (Answers A–C are incorrect).

4. **Answer: C**
This patient is having an acute depressive episode. He has been taking lithium for 5 years, which is long enough to derive any antidepressant effects. His lithium concentration is also within therapeutic range. Quetiapine is FDA indicated for depression associated with bipolar disorder (Answer C is correct). Its onset of action is more rapid than that of lamotrigine, which requires a slow titration to reach therapeutic doses (Answer B is incorrect). Unlike data for aripiprazole in unipolar depression, data for aripiprazole suggest it is not effective for bipolar depression (Answer A is incorrect). The efficacy of antidepressants in treating type I bipolar disorder is questionable, and treatment with an SNRI could lead to a switch to mania (Answer D is incorrect).

5. **Answer: A**
This patient has hypothyroidism, as indicated by her increased TSH concentrations. Her hypothyroidism was probably induced by lithium (Answer A is correct). Lithium-induced hypothyroidism is most common within the first 2 years of treatment. Although olanzapine can cause a metabolic syndrome with glucose intolerance and obesity, it would not increase TSH (Answer C is incorrect). Lithium-induced hypothyroidism is not dose-dependent, and the patient’s lithium concentration is on the lower side of the 0.6–1.0 mEq/L maintenance range (Answer B is incorrect). Ethinyl estradiol/drospirenone is not associated with TSH elevations (Answer D is incorrect).

6. **Answer: B**
This patient’s presentation and laboratory results are consistent with acute pancreatitis. Although the incidence of pancreatitis is rare, divalproex can cause this condition. Patients who develop pancreatitis while taking divalproex that resolves when the patient is no longer taking the agent should not be rechallenged (Answer B is correct). Neither aripiprazole nor lamotrigine is associated with pancreatitis (Answers A and C are incorrect). This patient’s lamotrigine dose should be lowered to prevent Stevens-Johnson syndrome. Despite lamotrigine’s temporal relationship with prednisone, it is probably not contributing to the current clinical picture (Answer D is incorrect).

7. **Answer: D**
The patient’s symptoms most closely resemble akathisia. The treatment of choice in this case is a lipophilic β-blocker such as propranolol (Answer D is correct). Benztropine 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.
(Answer A is incorrect). Benzodiazepines are effective for the treatment of akathisia, but they are not the best choice, given this patient’s history of alcohol use disorder (Answer C is incorrect). Dantrolene, a skeletal muscle relaxant, is used for neuroleptic malignant syndrome (Answer B is incorrect).

8. Answer: B
This patient has severe tardive dyskinesia. The symptoms involve the orofacial muscles and came on slowly after antipsychotics had been initiated. The symptoms improved with antipsychotic dose reduction. The antipsychotic of choice in patients with severe tardive dyskinesia is clozapine because of its low-to-nonexistent incidence of tardive dyskinesia (Answer B is correct). Chlorpromazine is also an FGA associated with tardive dyskinesia (Answer A is incorrect). Although risperidone is associated with a lesser degree of EPS, it can cause tardive dyskinesia (Answer D is incorrect). Although quetiapine has a low incidence of tardive dyskinesia, it is not the agent of choice in severe tardive dyskinesia, particularly in a patient whose therapy with an FGA (perphenazine) and an SGA (olanzapine) has previously failed (Answer C is incorrect).

9. Answer: D
This patient has diabetes, dyslipidemia, and obesity, all of which contribute to metabolic syndrome. With her family history of early coronary artery disease, an antipsychotic with a low incidence of metabolic syndrome is preferred. Of the antipsychotics listed, ziprasidone is the best choice (Answer D is correct). Olanzapine is associated with a high incidence of metabolic syndrome (Answer A is incorrect). Quetiapine has a lower incidence but can still cause metabolic abnormalities (Answer C is incorrect). Paliperidone is the major metabolite of risperidone and has a similar pharmacologic profile. Like risperidone, paliperidone is associated with an increased incidence of galactorrhea (Answer B is incorrect).

10. Answer: A
This patient has panic disorder. Benzodiazepines more rapidly treat the acute physical symptoms and fear that occur with panic disorder (Answer A is correct). Selective serotonin reuptake inhibitors such as paroxetine are first-line treatment for preventing panic attacks but take time to achieve full efficacy (Answer D is incorrect). Buspirone is not effective acutely for panic attacks (Answer B is incorrect). Hydroxyzine might offer some sedation, but it would not treat the underlying anxiety disorder (Answer C is incorrect).

11. Answer: D
An antidepressant is the first-line treatment for GAD. Venlafaxine has proven efficacy for GAD and may relieve this patient’s vasomotor symptoms (Answer D is correct). Fluoxetine is an effective choice for GAD but is a strong inhibitor of CYP2D6, which would decrease the efficacy of tamoxifen (Answer B is incorrect). Bupropion is also an inhibitor of CYP2D6 and is ineffective against most anxiety disorders (Answer A is incorrect). Pregabalin might be effective for GAD, but because clinical data are not as strong, it is generally used as a second- or third-line agent (Answer C is incorrect).

12. Answer: B
This patient primarily has difficulty with sleep onset and would benefit from an agent that decreases sleep latency and does not prolong sleep. Ramelteon is the only listed agent that produces these effects. Older adults can have difficulty with circadian rhythm, which a melatonin analog may help regulate. Ramelteon is also indicated for the treatment of chronic insomnia if needed for a prolonged period (Answer B is correct). Although eszopiclone decreases time to sleep, its longer half-life might result in hangover effects (Answer A is incorrect). Suvorexant also treats sleep maintenance, but it can also cause a hangover effect (Answer C is incorrect). Zolpidem received recent labeling changes for reduced doses and has reduced metabolism in older adults (Answer D is incorrect).

13. Answer: D
To avoid withdrawal symptoms, patients taking long-acting opioids should be tapered to the equivalent of methadone 30 mg/day or less before being changed to a buprenorphine regimen (Answer D is correct). Initiating a patient on buprenorphine at higher methadone doses could 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 (Answer B is incorrect). Patients taking long-acting opioids such as methadone should be changed to buprenorphine monotherapy before...
being advanced to buprenorphine/naloxone (Answer A is incorrect). Naltrexone monotherapy is inappropriate because it can precipitate withdrawal (Answer C is incorrect).

14. **Answer: A**

This patient has alcoholic hepatitis, as indicated by his AST and ALT values. Presumably, these would improve with abstinence. Liver function is intact, as evidenced by his albumin, PT, and platelet values. Naltrexone should be avoided in patients with a history of acute hepatitis or liver failure (Answer D is incorrect). Disulfiram should be used with caution in patients with active liver disease. Disulfiram also requires a strong commitment on the patient’s part to abstain from drinking and may be less effective. This patient has a history of several failed attempts (Answer C is incorrect). Chlordiazepoxide is used during acute alcohol detoxification but plays no role in maintenance therapy (Answer B is incorrect). The acamprosate dose should be reduced to 333 mg orally three times daily for a CrCl of 30–50 mL/minute/1.73 m$^2$ and is thus the most appropriate choice in this patient (Answer A is correct).

15. **Answer: A**

This patient’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 manage his nicotine cravings. Thus, his previous use of nicotine gum is not a true treatment failure. He has the two cardinal symptoms suggestive of depression (sad affect and anhedonia), making bupropion a reasonable choice (Answer A is correct). His myocardial infarction is not a contraindication to use of nicotine products; thus, nicotine gum could be added to bupropion if monotherapy fails (Answers B and C are incorrect). Coronary artery disease is not a contraindication to varenicline therapy, but given this patient’s likely concomitant depression, bupropion is a better fit (Answer D is incorrect).