Chapter 91: Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 67, Anxiety Disorders.

KEY CONCEPTS

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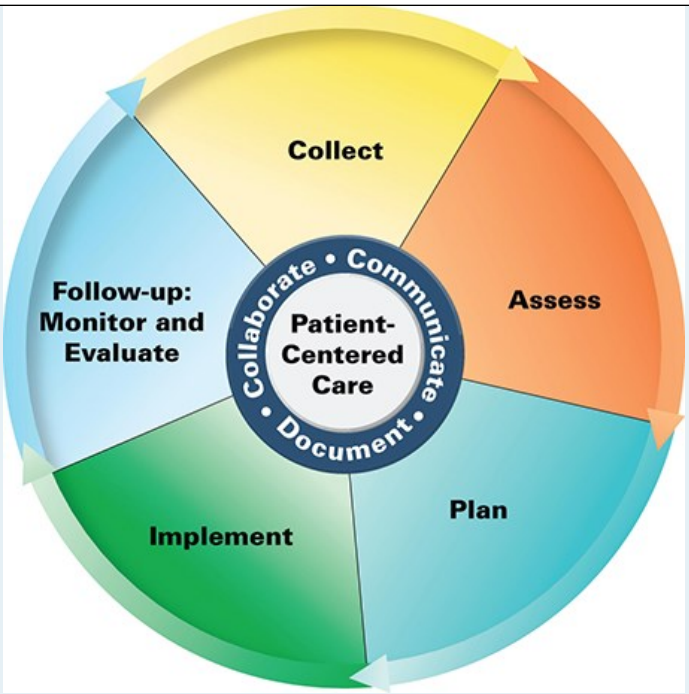
1. Trauma-focused cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing are the most effective nonpharmacologic methods to reduce symptoms of posttraumatic stress disorder (PTSD).
2. The selective serotonin reuptake inhibitors (SSRIs) and venlafaxine at moderate to high dose are considered first-line treatments for PTSD.
3. An adequate trial of SSRIs in PTSD is 8 to 12 weeks.
4. Patients with PTSD who respond to pharmacotherapy should continue treatment for at least 12 months.
5. CBT with behavioral techniques (eg, exposure and response prevention [ERP]) is the most common initial nonpharmacologic treatment of choice in obsessive-compulsive disorder (OCD).
6. Moderate-to-high dose SSRIs are the medication of choice for the treatment of OCD.
7. Clomipramine, a tricyclic antidepressant (TCA) with strong serotonin (5-HT) reuptake inhibition, is a second-line treatment option for OCD.
8. An adequate antidepressant trial for OCD treatment is 8 to 12 weeks.
9. Augmentation of SSRI treatment of OCD with low-to-moderate doses of antipsychotics may be helpful.
10. Medication taper can be considered after 1 to 2 years of treatment in patients with OCD.

PATIENT CARE PROCESS

Patient Care Process for Posttraumatic Stress Disorder and Obsessive-Compulsive Disorder



Collect

- Patient characteristics (eg, age, sex, pregnancy status)
- Patient medical history (personal and family, include first-degree relatives' response to medication)
- Social history (eg, tobacco use/ethanol use/substance use/sexual activity)
- Current medications including OTC use, herbal products, dietary supplements, and prior psychiatric medication use
- Patient health preferences, beliefs, and treatment goals
- Objective data
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
    - Lipid panel and A1c or fasting blood sugar if starting antipsychotic therapy
    - Electrocardiogram (ECG) if starting a tricyclic antidepressant (TCA) in a patient with cardiovascular disease, patient <18 or >40 years of page, or with other risk factors for QT prolongation (eg, electrolyte abnormalities, concomitant medications with the potential to prolong the QT)
    - Validated rating scale score (eg, Clinician Administered PTSD Scale [CAPS] or Yale-Brown Obsessive-Compulsive Scale [Y-BOCS])
    - Results of any pharmacogenomics testing

Assess

- Target symptoms (eg, intrusion, avoidance, reactivity, mood/cognition for PTSD and obsessions and/or compulsions for OCD) using CAPS, Y-BOCS, or other rating scale assessments
- Functional impairment/quality of life
- Sleep hygiene

- Psychotic symptoms
- Engagement in psychotherapy
- Medication adherence
- Ability/willingness to utilize and pay for pharmacotherapy or engage in psychotherapy
- Ability/willingness to return to clinic for continued regular symptom assessment
- Need to alter treatment plans due to results of pharmacogenomics testing

Plan*

- Pharmacotherapy regimen including specific medication, dose, route, frequency, onset of action, and duration (see Fig. 91-1, Tables 91-1 through 91-4)
- Monitoring parameters including efficacy (eg, rating scale score, sleep, other symptoms such as irritability, functional impairment, symptom diary) and safety (eg, suicidal ideation, adverse effects including insomnia, worsening anxiety or depression, gastrointestinal distress, sexual dysfunction, agitation); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, lifestyle modification, onset of action, treatment duration, medication specific information, medication administration technique; see Fig. 91-1 and Tables 91-2, 91-3, and 91-5)
- Self-monitoring for changes in PTSD/OCD symptoms, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, substance use treatment)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, CAPS/Y-BOCS or other rating scale assessments, adherence assessment, adverse effect assessment)
- Engage caregiver/family in treatment plan, if possible, and with patient permission

Follow-up: Monitor and Evaluate

- Improvement in rating scale scores of PTSD/OCD symptoms
- Presence of medication related adverse effects (eg, sexual dysfunction, insomnia)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate sleep hygiene
- Reevaluate effectiveness of psychotherapy
- Assess risk for suicidality

**Collaborate with patient, caregivers, and other healthcare professionals.*

BEYOND THE BOOK

BEYOND THE BOOK

PTSD

Prior to class visit the website PTSD: National Center for PTSD on the US Department of Veterans Affairs website at: www.ptsd.va.gov. Expand the section "Understand PTSD" then "Types of Trauma" to review one or two types of trauma (eg, war and combat, violence and abuse, disaster and terrorism.)

On the left-hand side menu, visit the section "For Providers" and complete the following steps:

1. Click on Assessment
2. Click on Adult Self-Report
3. Review the following screening tools: The PTSD Checklist for *DSM-5* (PCL-5)
4. Work with a friend or partner to role play and practice administering the PCL-5

This activity is intended to build your awareness of different types of traumas that patients may experience as well as familiarize yourself with the types of symptoms that patients are screened for when considering a diagnosis of PTSD.

OCD

Identify a mobile-app that may help manage OCD and related symptoms (eg, nOCD, GGOC, Headspace). Evaluate the mobile-app from the perspective of a patient with OCD and write a brief review for this application (eg, a single paragraph). Consider the following questions (you do not need to address each item):

- What symptom(s) is this mobile-app intended to help?
- How interactive is the mobile-app in giving feedback to the end user?
- Can the mobile-app be personalized for the end user?
- Do you foresee the mobile-app content and delivery methods accomplishing its purpose?
- Is there scientific research that demonstrates its effectiveness?
- Describe the patient population for which this mobile-app is best suited.

This activity is intended to build your awareness of the growing interest and use of mobile health technology devices to empower patients in self-management of their mental health.

INTRODUCTION

Traumatic or stressful events (eg, wars, terrorist attacks, natural disasters, pandemics, robbery, physical or sexual assault) can lead to development of posttraumatic stress disorder (PTSD).[1] Initially diagnosed in veterans of war, PTSD is now acknowledged as a significant psychiatric illness in the civilian population and among deployed service personnel of the Afghanistan and Iraq campaigns in whom the suicide rate has escalated.[1,2] In clinical practice, PTSD continues to be poorly recognized and diagnosed.[3] Because of its co-occurrence (greater than 50%) with anxiety disorders, depression, substance use, and traumatic brain injury, the overlapping symptoms can lead to diagnostic uncertainty.[3] PTSD has been shown to increase the risk of lifetime suicide attempt.[3-7] Advances in the science and treatment of PTSD can assist clinicians in all fields to screen for a history of trauma and effectively manage PTSD.

Intrusive obsessive thoughts and compulsive ritualistic behaviors characterize obsessive-compulsive disorder (OCD),[1] with symptoms potentially being severe enough that they impair functioning in social, family, and work settings, and decrease overall quality of life (QOL). Comorbid depression is common with OCD, with approximately 40% of patients having a history of major depression during their lifetime.[6] A diagnosis of OCD is also associated with an increased risk of suicide, with a mean of 13.4% (range 1%-46.3%) of patients reporting a previous history of suicide attempt. Increased understanding of symptom dimensions and treatment response can improve QOL in patients suffering from OCD.

EPIDEMIOLOGY

Within the US population, the estimated lifetime prevalence of PTSD is 8.7%,[1] whereas the lifetime prevalence of OCD has been estimated at 2.3%.[8]

PTSD is associated with the incidence of trauma,[1] with the most frequently reported traumatic events in the United States being assault (physical and sexual) with a 52% lifetime prevalence and accidents or fires with a 50% lifetime prevalence.[3] The conditional probability of developing PTSD differs between sex and type of trauma. The probability of developing PTSD for males and females after rape is 65% and 46%, after physical assault 2% and 22%, and after an accident are 6% and 9%, respectively.[7,9] Prevalence of PTSD is consistently higher among females (10.4%-12.3%) than males (5%).[7] Gender roles, genetic predispositions as well as hormonal influences may put females at higher risk of PTSD.[10] While the age of onset and course of PTSD are variable, it is important to note that PTSD can occur at any age, but most cases occur before the age of 40 years. The presentation is also not predictable, because symptoms are impacted by the duration and intensity of the trauma, the presence of other psychiatric disorders, and early posttrauma interventions.[3] Genetic factors can increase vulnerability to PTSD if an individual is exposed to a traumatic event. Lastly, veterans and those whose jobs increase the risk of traumatic exposure (eg, firefighters, first responders, police) have higher rates of PTSD.[1,3]

The epidemiology of OCD is also influenced by age and sex. The age of onset has a bimodal distribution peaking in late childhood/early adolescence and then again in early adulthood.[11,12] In males, the onset of illness is more frequently seen during childhood/adolescence versus early adulthood in females. The annual US prevalence of OCD is greater in females (1.8%) versus males (0.5%).[7] Patients with childhood-onset OCD often have concurrent ADHD and tic disorders, whereas mood disorders, other anxiety disorders, and obsessive-compulsive personality disorder are common comorbidities in adult-onset OCD.[1] Greater than 50% of patients with Tourette Syndrome have OCD symptoms, and around 30% will eventually be diagnosed with OCD.[13] Patients with eating disorders have a wide range of reported comorbid OCD.[14] Heredity is stronger when there is an early age of onset or comorbidity with tic disorder.[1] The average delay in time to appropriate treatment for OCD following symptom onset is nearly 8 to 10 years[12] as OCD is a disorder that is poorly recognized and patients often do not seek treatment until late during illness.

ETIOLOGY

The exact etiologies of PTSD and OCD are unknown; however, it is likely that abnormalities in several areas of brain functioning interact to cause these chronic disorders. Genetics may play a role in PTSD and OCD expression, but environmental factors are also involved. A number of genetic markers for PTSD are under evaluation, including genes associated with the hypothalamic-pituitary-adrenal (HPA) axis (eg, FKBP5), the amygdala-medial prefrontal cortex (mPFC)-hippocampus circuit, and the serotonin transporter.[15-18] Given the heterogeneity and individual differences in course and presentation of PTSD, recent studies have focused on gene by environment (G x E).[16,18] There is increasing evidence of immune dysregulation in PTSD, but it is unknown if it is a predisposing factor versus comorbidity related.[18] The behaviors in OCD are also heterogeneous, suggesting OCD is a polygenic disorder.[13,19-21] Potential genes include those affecting serotonin (5-HT), dopamine (DA), and glutamate.[13] An association with the D_2 receptor gene has been identified in OCD with tics and other potential genes associated with OCD include 5-HT transporter and receptors (eg, 5-HT_{1D} beta, 5-HT_{2A}, and 5-HT_{2C}). Research on the role of glutamate in OCD has identified genes of interest including glutamate-related synapse (*SAPAP/DLGAP*); glutamate transporter (*SLC1A1*); and N-methyl-D-aspartate (NMDA) receptor genes (*GRIN2B* and *GRIK*).[13,19,20] Twin studies found higher concordance rates in monozygotic versus dizygotic twins, suggesting an approximate 48% OCD heritability. Some subtypes, such as early-onset OCD with tics, may have higher heritability.[20,21] Further understanding of the roles genetics and the environment play in the development of PTSD and OCD may impact future treatment strategies and are current research areas.

In children, the occurrence of sudden onset OCD and chronic tic disorder following a streptococcal infection has been reported and previously labeled

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS).[20,21] Controversy currently exists as to whether PANDAS should be characterized as a subtype of OCD. Although most patients with OCD do not have a streptococcal etiology, an accurate medical history regarding onset of illness is imperative because specific treatment strategies are indicated. More recently, PANDAS has been broadened to pediatric acute-onset neuropsychiatric syndrome, or PANS, to include OCD symptoms that start after nonstreptococcal infections.

Substance/medication-induced OCD has been described with stimulants including cocaine, amphetamines, and methylphenidate. Furthermore, cases of OCD-like behaviors (eg, pathologic gambling) have been described with dopamine agonists (eg, ropinirole, pramipexole).[13]

PATHOPHYSIOLOGY

Research findings in the areas of neuroendocrinology, neurobiology, and neuroimaging have advanced theories on the pathophysiology of OCD, and PTSD. Neuroendocrine changes in the HPA axis are implicated in the pathophysiology of PTSD. The neurobiology of PTSD focuses on alterations in fear learning, threat detection, executive function, and emotional regulation, as well as contextual processing.[3] Dysfunction in the cortico-striato-thalamo-cortical (CSTC) circuit is implicated in OCD.[20,21] As reviewed in Chapter 90, "Generalized Anxiety Disorder, Panic, and Social Anxiety Disorders," data from neurochemical and neuroimaging studies indicate that the modulation of normal and pathologic anxiety states is associated with multiple regions of the brain (eg, amygdala, hippocampus, thalamus, and prefrontal cortex).[3] Abnormal function in several neurotransmitter systems, including norepinephrine (NE), γ-aminobutyric acid (GABA), glutamate, DA, and 5-HT, may affect the manifestations of OCD and PTSD.[16,22,23]

Neuroendocrine Theories

Neuroendocrine studies provide data that abnormalities occurring pretrauma, during trauma, and posttrauma contribute to PTSD. Trauma exposure is linked to abnormal HPA activity and cortisol patterns.[24] Normally the immediate reaction to stress occurs as an automatic response from the amygdala to the sympathetic and parasympathetic systems and the HPA axis.[22] The release of corticotropin-releasing factor (CRF) stimulates cortisol secretion from the adrenal gland and both catecholamines and cortisol levels rise in tandem. Cortisol then reduces the stress response by tempering the sympathetic reaction through negative feedback on the pituitary and hypothalamus[22] with both systems returning to normal after a few hours.

Data implicate a role for the neuropeptides CRF and neuropeptide Y (NPY) in PTSD, as patients with PTSD have a hypersecretion of CRF but demonstrate subnormal levels of cortisol at the time of trauma and then chronically.[22] Lower plasma cortisol concentrations were associated with greater severity of PTSD symptoms in nonmilitary patients[23] and dysregulation of the HPA axis is postulated to be a risk factor for eventual development of PTSD.[22] The NPY system is a mediator between exposure to stress and development of resilient versus maladaptive responses and the role of NPY in improving resilience is a continued area of research interest.[25]

Neurochemical Theories

Several neurotransmitters may be involved in the pathophysiology of PTSD as 5-HT, NE, and glutamate are associated with the processing of emotional and somatic contents of memories in the amygdala.[23] Alterations in these neurotransmitters are linked to alterations in amygdala activity.[3] The amygdala is involved in processing emotions, and acquiring, expressing, and regulating fear and traumatic memories, including fear conditioning.[24] The medial prefrontal cortex (mPFC) and hippocampus are involved in contextual processing. The noradrenergic theory posits that the autonomic nervous system of patients with anxiety is hypersensitive and overreacts to stimuli. The alarm center, the locus ceruleus, releases NE to stimulate the sympathetic and parasympathetic nervous systems. Hyperactive noradrenergic signaling in patients with PTSD is a consistent research finding and includes increased 24-hour catecholamine excretion.[23] Glutamate signaling abnormalities may result in distortion of amygdala-dependent emotional processing under stress.[22,23] Dysregulation of the processing of sensory input and memories may contribute to the dissociative and hypervigilant symptoms in PTSD. Abnormalities of GABA inhibition may lead to increased awareness or response to stress, as seen in PTSD.[26]

Both 5-HT and DA are implicated in the pathogenesis of OCD. Selective and potent serotonin reuptake inhibitors have consistently been shown effective for symptoms of the illness,[27] especially at higher doses. The most commonly studied serotonin receptors in OCD are 5-HT_{2A}, 5-HT_{1B}, and 5-HT_{2C}.[28] Dopamine dysregulation may also contribute to some forms of OCD, as neurologic symptoms (eg, tics) are part of the clinical presentation in

some patients with OCD and Tourette Syndrome, a disorder of DA function.[1,13] Additionally use of dopamine agonists can worsen OCD symptoms, whereas augmentation with antipsychotics may improve symptoms in patients with OCD who are partially responsive to selective serotonin reuptake inhibitors (SSRIs).[13] More recently glutamate has become another neurotransmitter of interest in OCD, especially in genetic research.[19]

Neuroimaging Studies

Neuroimaging studies suggest that certain areas of the brain are altered by psychological trauma. In PTSD, most functional neuroimaging studies have involved the amygdala, mPFC, dorsal anterior cingulate cortex (dACC), insula, and hippocampus.[3] Findings of increased activation of the amygdala after trauma-related imagery, sounds, or smells indicate that this structure plays a role in the persistence of traumatic memory.[29] Decreased amygdala activation is correlated with resilience to PTSD and response to CBT. Historically, studies have suggested patients with PTSD have reduced amygdala volume; however, a recent study suggested instead that smaller amygdala volume is related to exposure to trauma and not necessarily PTSD.[24] Hypofunctioning of the mPFC is theorized to prevent extinction of fear in patients with PTSD, and is associated with impairments in extinction recall, abnormalities in processing contextual information, and impairments in safety-signal learning.[3] Hyperresponsivity of the dACC, amygdala, and the insula may correlate with impaired response to emotional or salient stimuli or impaired threat detection. Not all magnetic resonance imaging (MRI) studies show reduced hippocampal volume in PTSD; however, reduced hippocampal volume has been linked to reexperiencing symptoms in PTSD.[24] In twin studies, the unaffected twin of patients with PTSD also demonstrated smaller hippocampi compared with twins without PTSD that may suggest that lower hippocampal volumes are likely a precursor associated with vulnerability for subsequent PTSD development.[22]

Neuroimaging studies consistently show evidence that dysfunction in the CSTC circuit, which regulates self-control, is associated with OCD.[13,19-21] The role of neuromodulation treatment in OCD supports the CSTC model.[21] Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies in OCD have shown increased activity in the anterior cingulate cortices, and different patterns of activation in the caudate.[11] Evidence suggests that lower pretreatment activity in the orbitofrontal cortex predicts a better response to SSRIs and improved fluvoxamine response has been correlated with abnormalities in the posterior cingulate cortex.

CLINICAL PRESENTATION

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) made several changes to the classification of anxiety and related disorders[1] with individual chapters for anxiety disorders, trauma- and stressor-related disorders, and obsessive-compulsive and related disorders. Generalized anxiety disorder, panic disorder, and social anxiety disorder are discussed in Chapter 90.

Posttraumatic Stress Disorder

Exposure to a traumatic event is required for a diagnosis of PTSD[1] in that the person must have witnessed, experienced, or been confronted with a situation that involved definite or threatened death or serious injury, sexual violence, or possible harm to self or others. Some examples of traumatic events include physical attacks by an intimate partner, severe traffic accidents, military combat, natural disasters, being held hostage, child sexual abuse, witnessing a murder or injury of another, and learning of a traumatic event that happened to a close family member or friend. While systematic reviews have yet to be conducted, the impact of the coronavirus (COVID-19) pandemic on PTSD has been published across populations, including healthcare workers experiencing PTSD and young adults with worsening PTSD symptoms.[30,31]

The resulting PTSD symptoms include persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, numbing of general responsiveness, and persistent symptoms of hyperarousal.[1] Patients must have at least one intrusion symptom, at least one symptom of avoidance of stimuli associated with the trauma, at least two symptoms of negative alterations in cognition and mood, and at least two symptoms of increased arousal. Symptoms from each category need to be present for longer than 1 month and cause significant distress or impairment in functioning. Most persons diagnosed with PTSD also meet criteria for another psychiatric disorder, most commonly mood, anxiety, and substance use disorders.[1,4,32]

Anxiety and dissociative symptoms (eg, absence of emotional responsiveness, derealization, inability to recall important features of the trauma) emerging within 1 month after exposure to a traumatic stressor are classified as Acute Stress Disorder (ASD).[1] Symptoms of ASD are experienced

during or immediately after the trauma, last for at least 3 days, and resolve within 1 month. The severity and course of illness is fluctuating and often worsens, with life stressors.

CLINICAL PRESENTATION: Posttraumatic Stress Disorder

Intrusion Symptoms

- Recurrent, intrusive distressing memories of the trauma
- Recurrent, disturbing dreams of the event
- Feeling that the traumatic event is recurring (eg, dissociative flashbacks)
- Physiologic reaction to or psychological distress from reminders of the trauma

Avoidance Symptoms

- Avoidance of conversations, thoughts, or feelings about the trauma
- Avoidance of people, places, or activities that are reminders of the event

Persistent Negative Alterations in Thinking and Mood

- Inability to recall an important aspect of the trauma
- Estrangement from others
- Restricted affect
- Negative beliefs about oneself
- Distorted beliefs causing one to blame others or themselves for the trauma
- Negative mood state

Hyperarousal Symptoms

- Decreased concentration
- Easily startled
- Self-destructive behavior
- Hypervigilance
- Insomnia
- Irritability or anger outbursts

Specifiers

- Dissociative symptoms: depersonalization or derealization
- With delayed expression: full criteria are not met until at least 6 months posttrauma

Data from References 1 and 32.

Obsessive-Compulsive Disorder

The diagnostic criteria for OCD require the presence of obsessions and/or compulsions that are severe enough to cause marked distress, to be time-consuming (occupy more than 1 hr/day), or cause significant impairment in social or occupational functioning.[1] An obsession is a recurrent, persistent idea, thought, impulse, or image that is experienced as intrusive and inappropriate and produces marked anxiety. A compulsion is defined as a repetitive behavior or act generally performed in response to an obsession. While it is most common for patients to have both obsessions and compulsions, some may only have one or the other. Diagnostically, the compulsive behavior is not pleasurable and is designed to prevent discomfort or the occurrence of a dreaded event that is often unknown and part of the obsession. Therefore, compulsive behaviors are usually performed according to certain rules or in a stereotyped fashion. Common symptom dimensions involve cleaning (eg, contamination obsessions and cleaning compulsions), symmetry (eg, symmetry obsessions and ordering or arranging compulsions), forbidden or taboo thoughts (eg, violent, sexual, or religious obsessions and related compulsions), and harm (eg, fears of causing harm or superstitions and related compulsions).[1,12] For example, patients obsessed with the fear of causing harm (eg, inadvertently hitting a pedestrian), may cause them marked distress and lead to repetitive checking (eg, driving past crosswalks to check for injured pedestrians).[12]

There are two specifiers for OCD related to the degree of insight and the presence of tic-related symptoms.[1] While individuals vary widely in their insight into the irrationality of their obsessive-compulsive symptoms, most will have good or fair insight. The addition of an insight specifier allows the diagnosis to include individuals with poor to absent insight such as those with comorbid psychosis.[12] Individuals with tic-related OCD appear to differ from those with non-tic-related OCD in terms of etiology, illness course, symptom presentation, comorbidities, heredity, and pharmacotherapy response.[1]

CLINICAL PRESENTATION: Obsessive-Compulsive Disorder

Obsessions

- Repetitive thoughts (eg, feeling contaminated by germs, fears of harming others)
- Repetitive images (eg, recurrent sexually explicit pictures)
- Repetitive urges (eg, need for symmetry or putting things in specific order)

Compulsions

- Repetitive activities (eg, hand washing, need to ask, need to confess)
- Repetitive mental acts (eg, counting excessively, repeating words silently, praying)

Specifiers

- Insight: good or fair insight, poor insight, or absent insight/delusional beliefs
- Related to a tic disorder

Data from References 1 and 12.

The diversity of OCD symptoms can obscure an accurate diagnosis as patients often present in a seemingly incongruous manner to non-mental health clinicians for other complaints—dermatologists for eczema or chapped skin, pediatricians for parental concerns over a child's compulsive hand washing, neurologists for tics, or dentists for gum lesions from compulsive teeth brushing.[12] Because patients recognize their compulsive behavior as illogical or irrational, they also can become extremely adept at denying symptoms, disguising their rituals, and concealing their illness from friends and family.[1]

It is important to note that OCD is a chronic illness in most patients, with symptom severity varying in intensity over time,[12] resulting in a significantly impaired QOL.

TREATMENT

Posttraumatic Stress Disorder

Desired Outcomes

The short-term goal of therapy in the management of PTSD is a reduction in core symptoms (eg, intrusive reexperiencing, avoidance, and hyperarousal). Additional goals include improvement in disability, concurrent psychiatric conditions, resilience, and QOL with the long-term goal of PTSD remission.

General Approach to Treatment

In general, individuals who seek treatment acutely after a trauma and are in intense distress should receive therapy based on their presenting symptoms (eg, a nonbenzodiazepine hypnotic for difficulty sleeping). Short courses of exposure-based, trauma-focused cognitive behavioral therapy (TFCBT) can be helpful to prevent chronic PTSD in patients with ASD or acute PTSD.[4] If symptoms (eg, hyperarousal, avoidance, dissociation, sleep difficulties, or depressed mood) persist for 3 to 4 weeks and the patient experiences marked social, occupational, and/or interpersonal impairment, they can be treated with pharmacotherapy, psychotherapy, or both. Many patients with PTSD will improve substantially with pharmacotherapy but retain some symptoms. Treatment regimens usually combine psychoeducation, psychosocial support and/or treatment, and pharmacotherapy; however, newer guidelines specifically emphasize the utility of individual trauma-focused psychotherapies.[3,5,33,34]

Nonpharmacologic Therapy

Psychotherapy can be used when a patient suffers from mild symptoms, in patients who prefer not to use medications, or in conjunction with medication in patients with severe symptoms to improve response.[5,35] Notably, current clinical practice guidelines emphasize the role of trauma-focused psychotherapy as the preferred treatment approach.[5,33,34] Patients who have experienced trauma should be educated that they can experience anxiety, depression, nightmares, and even flashbacks as a reaction to the event. Brief courses of individual trauma-focused psychotherapy, focusing on exposure or cognitive restructuring, near the traumatic event resulted in lower rates of PTSD 3 and 6 months later. Single-session critical incident stress debriefing has not shown to be effective in preventing development of PTSD and may cause harm.[3,5] Involving the patient in the selection of preferred treatment, especially in those that prefer prolonged exposure therapy, has demonstrated improved health-related QOL.[36]

1 Psychotherapies for treating PTSD include prolonged exposure, TFCBT, cognitive processing therapy (CPT), eye movement desensitization and reprocessing (EMDR), and psychoeducation.[4,5,35] The unique treatment EMDR involves the process of patients imagining exposure to the traumatic event, while simultaneously engaging in bilateral eye movements to assist with processing of this event, along with relaxation.[4] The cognitive and behavioral approaches of TFCBT and EMDR are more effective than stress management or group therapy to reduce symptoms of PTSD. Psychoeducation includes information about the disease state, treatment options, and avoidance of excessive use of alcohol and other used substances. Evidence suggests insomnia associated with PTSD benefits from CBT.[5] Novel nonpharmacologic approaches (eg, interpersonal psychotherapy, narrative exposure therapy, written narrative exposure, imagery, transcranial magnetic stimulation [TMS], neurofeedback, acupuncture, yoga, emotional freedom technique, virtual reality exposure, somatic experiencing, mindfulness therapies, and delivery methods [eg, telemedicine and other technology-based treatments]) are under study.[3,5,37]

Pharmacologic Therapy

2 Antidepressants are the major pharmacotherapeutic treatment for PTSD, in addition to also being effective for concurrent depression and anxiety disorders. SSRIs and venlafaxine are the first-line pharmacotherapy of PTSD[4-6,32,33,38,39,42,57]; however, the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) can also be effective despite their less favorable side-effect profiles (Table 91-1). Both sertraline and paroxetine are approved for the acute treatment of PTSD,[40,41] and sertraline is approved for the long-term (eg, 52 weeks) management of PTSD.[41] A number of

medications can be used as augmentation (eg, antiadrenergic agents, second-generation antipsychotics, and antiseizure medications).[4,5,42] Benzodiazepines are not effective for PTSD.[5,32-34,39] A number of treatment guidelines are published,[4,5,32-34,42] with Table 91-2 providing a summary of key points from the treatment guidelines for PTSD. An algorithm for the treatment of PTSD appears in Fig. 91-1.

FIGURE 91-1

Algorithm for the pharmacotherapy of posttraumatic stress disorder (PTSD). (SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.) *(Data from References 38 and 39.)*

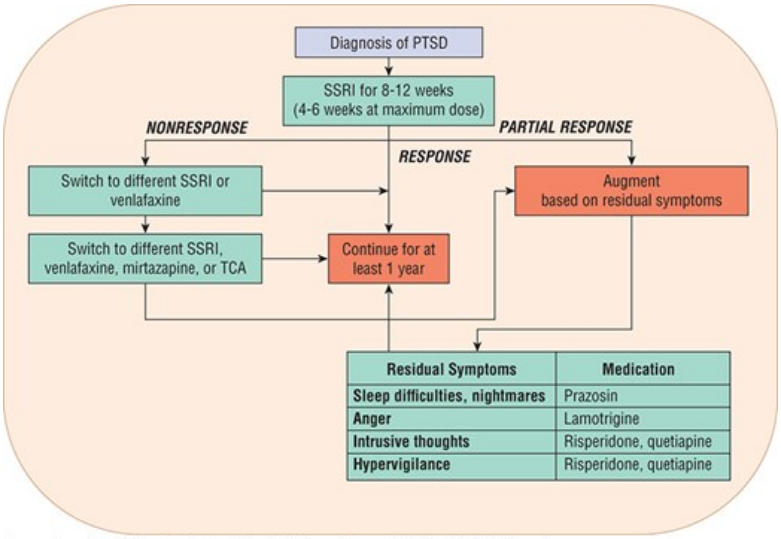


TABLE 91-1

Dosing of Antidepressants in the Treatment of PTSD

Medication	Brand Name	Initial Dose	Usual Range (mg/day)	Comments
SSRIs				
Fluoxetine	Prozac	10 mg daily	10-80[a]	
Paroxetine	Paxil, Pexeva	10-20 mg daily	20-50	Maximum dose is 60 mg daily[a]
Sertraline	Zoloft®	25 mg daily	50-100	Maximum dose is 200 mg daily[b]
Other Agents				
Amitriptyline	Elavil	25 or 50 mg daily	75-200[a]	
Imipramine	Tofranil	25 or 50 mg daily	75-200[a]	
Mirtazapine	Remeron	15 mg every night	30-60[a]	
Nefazodone	n/a	25-100 mg twice daily	150-600[a]	Product has a black box warning for hepatotoxicity
Phenelzine	Nardil	15 or 30 mg every night	45-90[a]	
Venlafaxine extended-release	Effexor XR	37.5 mg daily	75-225[a]	

[a]Dosage used in clinical trials but not FDA-approved.

[b]Dosage is FDA-approved.

PTSD, posttraumatic stress disorder; SSRIs, selective serotonin reuptake inhibitors; n/a, not applicable.

Data from References 5, 32, 30 and 41.

TABLE 91-2

Summary of Key Points in Treatment Guidelines for PTSD

Recommendations	Comments
First-Line Treatments	
• SSRIs: Fluoxetine, paroxetine, sertraline • SNRIs: Venlafaxine	At 4 weeks if there is partial response, continue for another 4 weeks. At 8 weeks, if no improvement, increase dose to maximum tolerated or switch to another first-line treatment
Second-Line Treatments	
TCAs: Amitriptyline, imipramine	The risk of adverse effects and potential for fatalities in a TCA overdose are higher than with SSRIs or SNRIs
Mirtazapine	
Augmentation with prazosin for sleep/nightmares	Not recommended in the VA guidelines ***for use in veteran population***
Third-Line treatments	
Augmentation with antiseizure medications or second-generation antipsychotics	The VA guidelines recommend against using risperidone as an augmenting agent secondary to metabolic adverse effects. There is insufficient evidence to support routine use of other second-generation antipsychotics or antiseizure medications
MAOIs: Phenelzine	Potential adverse effects and dietary restrictions limit use
Nefazodone	Risk for hepatotoxicity limits use

PTSD, posttraumatic stress disorder; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; VA, Veterans Affairs.

Data from References 4, 5 and 39.

Selective Serotonin Reuptake Inhibitors

The SSRIs pharmacologically enhance serotonergic functioning and large prospective guidelines document the efficacy and consistently recommend use of fluoxetine, sertraline, and paroxetine in the acute management of PTSD.[5,32-34,36,39] While a meta-analysis found that SSRIs were significantly better than placebo for the treatment of PTSD, the overall effect size was small.[43] Adverse reactions reported in patients with PTSD treated with SSRIs include gastrointestinal symptoms, sexual dysfunction, insomnia, and agitation. Additionally, long-term use of SSRIs (durations of 9-12 months) has been shown to be effective in preventing relapse.[4,42]

Other Antidepressants

The serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine has shown efficacy in PTSD. In a 12-week, placebo-controlled trial comparing venlafaxine extended-release and sertraline, venlafaxine was effective in reducing the avoidance/numbing and hyperarousal clusters of PTSD, whereas sertraline improved all PTSD symptom clusters.[44] The remission rates for venlafaxine extended-release were 30.2% after 12 weeks[44] and 50.1% after 6 months.[45] In one retrospective study, when compared with fluoxetine, sertraline, paroxetine, and topiramate, venlafaxine demonstrated higher 12-week acute phase remission rates, though additional studies are needed.[46]

Other antidepressants have been studied in controlled trials with mirtazapine considered a second-line agent in one guideline,[4] while others highlight insufficient data to recommend use.[5,32,37,42] Specifically, one recent prospective, placebo-controlled trial found mirtazapine did not reduce PTSD, depression, or insomnia symptoms among male combat veterans.[47] The TCAs amitriptyline and imipramine are considered second-line agents, whereas phenelzine and nefazodone are considered third-line antidepressants if therapeutic trials of SSRIs or venlafaxine have failed. Potential adverse effects or risks associated with these agents (eg, daytime drowsiness and toxicity in overdose with TCAs; dietary restrictions and potential medication interactions with MAOIs; or risk of liver failure with nefazodone) limit their use clinically.[4,5,35,42] Bupropion is not recommended in patients with PTSD due to poor quality of evidence, but this agent may be considered as a third-line option.[4,5,32]

Alternative Medication Treatments

Second-generation antipsychotics, α_1-adrenergic receptor antagonists, and antiseizure medications can be used as augmenting agents for persistent PTSD symptoms, in cases of partial response to SSRI therapy after 4 to 6 weeks, or for comorbidities.[4,32,39,42,48] Data on the efficacy of second-generation antipsychotics are conflicting with one study showing quetiapine monotherapy was generally well tolerated and associated with improvements in overall symptomology, reexperiencing, and hyperarousal.[49] Further, guidelines suggest second-generation antipsychotics may be useful in targeting intrusive symptoms,[4] whereas others advise against use due to insufficient evidence[5,32] or use with caution.[33] Any potential benefit must be considered in the context of risks, including metabolic complications. One meta-analysis supports risperidone use among the second-generation antipsychotics,[50] while other recent guidelines advise against use of any second-generation antipsychotic for PTSD due to limited evidence and adverse effect profile.[5,32]

Prazosin (an α_1-adrenergic receptor antagonist) can be useful in some patients with PTSD, with earlier studies showing that it may decrease nightmares and symptoms of hyperarousal, increase total sleep time and sleep quality, and improve core PTSD symptoms. When used for PTSD the daily doses start at 1 mg and may be increased as tolerated to 25 mg.[51] Its presumed mechanism of action is reduction of noradrenergic transmission.[51] In a more recent study, use of prazosin among veterans with chronic PTSD did not improve nightmares or sleep quality compared to placebo, though the study population may have selected patients who were less likely to respond to prazosin.[52] In light of this data, newer Veterans Administration guidelines cite prazosin effects to be similar to placebo and state there is insufficient evidence to recommend use of this agent in this population,[5] whereas other studies and guidelines continue to support prazosin use, when indicated.[53,54] Other pharmacologic options for persistent sleep disturbances are limited. Medications with sedative properties (eg, nefazodone, imipramine, mirtazapine, phenelzine, or second-generation antipsychotics) may be considered depending upon individual comorbidities.[5,39] Other therapies that may be useful for PTSD-related nightmares are discussed in the American Academy of Sleep Medicine Position Paper.[55]

Antiseizure medications can assist in reducing impulsive anger and can also be used in patients with comorbid bipolar disorder; however, the use of an antiseizure medication is not recommended as monotherapy. Some data support efficacy of lamotrigine and topiramate, though overall data with antiseizure medications are inconsistent.[4,5,32,39]

Dosage and Administration

Acute Phase

Symptoms of PTSD respond slowly to pharmacotherapy, and some patients never experience full resolution; therefore, SSRIs should be started 3 to 4 weeks after exposure to a trauma in patients with no improvement in their acute stress response. The initiation of an SSRI should be at a low dose with gradual titration upward as tolerated to moderate to high doses. Eight to 12 weeks is an appropriate duration of antidepressant therapy to

determine response.[4,38,42]

Continuation Phase

Many patients undergo psychotherapy during the continuation phase of therapy, and medication dosages can vary as patients deal with past traumatic experiences. During this phase, symptoms continue to improve. Six-month relapse prevention trials in patients responsive to fluoxetine or sertraline indicate low rates of relapse with SSRI therapy compared with placebo.[42]

Maintenance and Discontinuation

4 Patients with PTSD who respond to pharmacotherapy should continue treatment for at least 12 months.[4,38,42,56] If residual symptoms persist, medication therapy should be continued. The decision about when to discontinue therapy is based on response, relapse prevalence, presence of ongoing stresses, adverse effects, and patient preference. Once the decision is made to discontinue therapy, the medications should be withdrawn and tapered slowly over a period of at least 1 month to reduce the potential for relapse.

Special Populations

Adults are not the only population susceptible to PTSD, as children who experience stress and trauma (eg, sexual or physical abuse or loss of a parent) are predisposed to develop mood and anxiety disorders. For this patient population, SSRIs are the initial pharmacologic agents of choice[57]; however, psychotherapy (eg, TFCBT) is also a treatment option and studies are ongoing to assess the comparative efficacy and acceptance of psychotherapies for PTSD among children and adolescents.[58,59]

Patients with PTSD and co-occurring unhealthy substance use disorders also warrant careful consideration given the greater risk for attempted suicide.[60] Guidelines suggest this population may benefit from concurrent treatment of both PTSD and substance use disorder and trauma-focused therapies have demonstrated improvement in PTSD symptoms in this population.

Choosing Pharmacotherapy

The choice of pharmacotherapy should be individualized to the patient's presenting symptoms. Selection of SSRI or venlafaxine monotherapy is based on the patient's history of prior response, safety, and side-effect tolerability and is largely a trial-and-error process.[61] When selecting an agent, the clinician should consider the potential for adverse consequences in patients with comorbid conditions (eg, anticholinergic effects and weight gain with paroxetine in patients with benign prostatic hypertrophy or obesity) or adverse effects (eg, insomnia with fluoxetine in patients with sleep difficulties). Increased risk of suicidality should be considered in patients taking antidepressants who are under 25 years of age.

Currently there are no guidelines or articles that specifically address the use of pharmacogenomics testing in PTSD.[43] However, there are data that can help guide medication selection based on specific gene medication pairs for many of the antidepressants used in treating PTSD.[61] The Clinical Pharmacogenomics Implementation Consortium (CPIC) is a valuable resource for understanding dosing recommendations for these various medication and gene combinations.[62]

EVALUATION OF THERAPEUTIC OUTCOMES

During the acute phase of therapy, patients should be seen frequently. During months 3 to 6 of therapy, the patient can usually be seen monthly, and in months 6 to 12, visits can usually be extended to every 2 months. On each visit the patient should be asked about previously identified PTSD target symptoms as well as other symptoms including insomnia, suicidal ideation, anger outbursts, irritability, psychosis, ongoing trauma, and disability. The Clinician-Administered PTSD Scale (CAPS) can be used by the clinician to assess symptom severity at each visit.[5] Remission in patients with PTSD is defined as a 70% or greater reduction in symptoms. A 50% or greater reduction in symptoms is considered adequate response, while a 25% to 50% reduction in symptoms is considered partial response. Before deciding that a patient is not responsive to pharmacotherapy, the clinician should ensure patient adherence and that the medication trial has been adequate in both dose and duration.

Many patients with PTSD are sensitive to the adverse effects of medications and should be monitored carefully for adverse reactions that can delay

dose escalation or cause the patient distress. See Chapter 88 for details on monitoring antidepressants. Routine assessment of the metabolic profile is necessary if a second-generation antipsychotic is used concurrently (see Chapter 87).[4,33] When pharmacotherapy is discontinued, patients should be seen more frequently and monitored carefully for signs of relapse or withdrawal.

TREATMENT

Obsessive Compulsive Disorder

Desired Outcomes

Major goals of therapy for OCD include reduction in the frequency and severity of obsessive thoughts and time spent performing compulsive acts.[63] Treatment for OCD generally does not eliminate obsessions or compulsions, but patients can feel remarkably improved with partial resolution of symptoms. Patients typically experience waxing and waning symptoms with only 20% going on to achieve full remission.[1] Optimal treatment increases psychosocial and occupational functioning and improves overall QOL.[63] Efforts should be made to minimize adverse medication events and prevent interactions.

General Approach to Treatment

It is important at the outset of therapy to identify and document the specific target symptoms for pharmacotherapy. Rating scales can be used to measure symptom severity at baseline and during treatment to ascertain the degree of improvement. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is the most widely used clinician-administered OCD rating scale. A QOL scale can assist the clinician in identifying other areas to target for treatment (eg, depression and reduced physical well-being).[63,64]

The FDA has approved five antidepressants for the management of OCD: clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline. First-line therapy for OCD includes CBT alone, SSRI monotherapy, or the combination of CBT and an SSRI.[63,64] The choice of therapy is based on clinical judgment, symptom severity, and patient preferences[63]; however, CBT has been largely found to be more effective compared to SSRI monotherapy.[65,66] Patients unable to participate in CBT or with a prior history of medication therapy response should be treated with SSRI monotherapy.[63] Combined CBT and SSRIs is recommended in patients who do not respond to SSRI monotherapy or in those with severe OCD. If a combination of CBT and an SSRI at maximum tolerated dose is unsuccessful, subsequent management options include intensifying CBT, switching to an alternate SSRI, switching to clomipramine, or augmenting with either clomipramine or an antipsychotic.[12,27]

Table 91-3 provides a summary of key points from the treatment guidelines for OCD. Although some OCD symptoms can improve over the first 2 to 6 weeks of therapy, an adequate trial is considered 8 to 12 weeks.[12,26,67]

TABLE 91-3

Summary of Key Points in Treatment Guidelines for OCD

Recommendation	Comments
First-Line Treatments	
CBT alone	13-20 sessions
SSRI alone	8-12 weeks, at least 4-6 weeks at maximum tolerated dose
CBT + SSRI	If monotherapy with CBT or SSRI alone does not provide adequate response, combination therapy with CBT + SSRI should be tried before augmentation with another pharmacologic agent
Second-Line Treatments	
Switch to another SSRI or clomipramine	
Augmentation with antipsychotic	Aripiprazole and risperidone are preferred second-generation antipsychotics for OCD treatment
Switch to venlafaxine	
Third-Line Treatments	
Switch to another antipsychotic augmenting agent	
Switch to duloxetine or mirtazapine	
Augmentation of SSRI with clomipramine	Citalopram, escitalopram, and sertraline have less risk to cause clinically significant medication interactions with clomipramine
Maintenance and Discontinuation Phase	
After 1-2 years, gradual taper over several months	
Periodic CBT booster sessions for 3-6 months	

CBT, cognitive behavioral therapy; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor.

Data from References 4 and 63.

Nonpharmacologic Therapy

5 Cognitive behavioral therapy with behavioral techniques (eg, exposure and response prevention [ERP]) is the most common initial nonpharmacologic treatment of choice in OCD and is largely considered to be more efficacious than pharmacotherapy.[12,36,66,68] It is preferred for motivated patients, particularly children and adolescents, with both mild OCD symptoms and psychiatric comorbidities, and in those with a desire to avoid medications.[11,12,63,68] Additionally, CBT offers flexibility in dosing (eg, weekly or intensively) and format (eg, individual, group, with or without family involvement).[12,68] Furthermore, family psychoeducation to minimize family accommodation (eg, adaptation of family routines that facilitate ritualistic compulsions) should be integrated into treatment plans to minimize the patient's functional impairment, family conflict/distress, and disruptive behavior to facilitate improved treatment response.[69]

Other nonpharmacologic options for OCD include neuromodulatory approaches (eg, deep brain stimulation [DBS], TMS, and electroconvulsive therapy [ECT]) and ablative neurosurgery for severely symptomatic patients as a treatment of last resort.[12,27] DBS is FDA-approved as a humanitarian device for severe, treatment-resistant OCD.[64] Despite the FDA clearing one TMS device for treatment of OCD, the significant heterogeneity across published study designs and outcomes calls for careful interpretation and application.[70] Preliminary data regarding ECT are promising but still inconclusive to support routine use.[27] While these alternatives may be effective in some patients, uncertainties regarding optimal stimulation site and settings for these neuromodulatory approaches likely contribute to heterogeneity in outcomes.

Pharmacologic Therapy

6 7 As a class, SSRIs are the medications of choice for patients with OCD,[63] and while not all are FDA-approved, citalopram and escitalopram have also shown efficacy in reduction of OCD symptoms.[12,66] Clomipramine, a TCA with strong 5-HT reuptake inhibition, is a second-line treatment option.[71] Benzodiazepines should not be used to treat OCD-related obsessions and compulsions.[27,63]

Antidepressant Medications

Current evidence indicates that 5-HT is important for the antiobsessional effects of these medications.[72] Pharmacologically, SSRIs and clomipramine inhibit 5-HT reuptake into the presynaptic neuron, making more 5-HT available to postsynaptic receptors and reducing formation of the 5-HT metabolite 5-hydroxyindoleacetic acid. Although other nonclomipramine TCAs (eg, amitriptyline, imipramine, and nortriptyline) inhibit 5-HT reuptake, they are less potent and selective. Prolonged exposure to increased amounts of 5-HT after chronic antidepressant treatment (2-3 weeks) leads to altered responsiveness of postsynaptic 5-HT receptors or presynaptic autoregulatory receptors that govern 5-HT release in specific brain regions. An improvement in obsessional symptoms may correlate with plasma concentrations of clomipramine but not desmethylclomipramine, the metabolite of clomipramine with less selectivity for 5-HT reuptake inhibition.[73]

Most experts agree that SSRIs are better tolerated than clomipramine.[12] Table 91-5 details the monitoring of SSRI and clomipramine pharmacotherapy in patients with OCD. Clomipramine is more likely to cause sedation, anticholinergic side effects and weight gain, however, is less likely than SSRIs to cause insomnia, akathisia, nausea, and diarrhea. Regardless of the specific medication used, antidepressant side effects can be dose related and worse with faster dose escalation.

The SSRIs are effective in the treatment of OCD with almost half (40%-60%) of patients achieving a response.[12] Well-designed trials comparing these medications with placebo in head-to-head comparative trials, and meta-analyses have established that fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram are equally effective.[27,66] However, the literature is conflicting as to whether clomipramine is more effective than the SSRIs.[12,27,66]

Venlafaxine and duloxetine, 5-HT and NE reuptake inhibitors, and mirtazapine may also be effective for OCD.[27] Therefore, these antidepressants can be considered second- or third-line therapy options.[4] See Table 91-3.

Pharmacokinetics

Clomipramine is rapidly absorbed after oral administration[71] with maximum plasma concentrations occurring within 2 to 6 hours. Clomipramine is

highly protein-bound (97%) in the blood and has a half-life of 19 to 37 hours. It is metabolized to an active metabolite, desmethylclomipramine, which inhibits NE reuptake. See Table 91-4 for information on monitoring clomipramine plasma levels. The pharmacokinetics of SSRIs is discussed in Chapter 88. It is important to note that since clomipramine and the SSRIs are extensively metabolized in the liver, patients with significant liver disease should be prescribed these medications cautiously and in lower doses than those without liver disease. Additionally, increased plasma concentrations of paroxetine occur in subjects with renal impairment necessitating a reduced initial dose.[40] For older patients, little information is available regarding pharmacokinetic changes; therefore, medication selection should be based on history of response and adverse effect profile, with treatment initiated at low dose, which is then increased slowly, with vigilant monitoring for adverse effects.[38,63]

Adverse Effects

When selecting pharmacotherapy, the clinician should consider medication specific adverse effects such as QTc prolongation risk with citalopram and escitalopram; anticholinergic effects and weight gain risk (eg, with paroxetine in patients with benign prostatic hypertrophy or obesity); insomnia risk with fluoxetine in patients with sleep difficulties; increased risk of suicidality in patients under 25 years of age taking antidepressants; and medication interaction risk for which citalopram, escitalopram, and sertraline have the least potential for cytochrome P450 (CYP450) isoenzyme inhibition (see Chapter 88).[27]

Risks to consider with clomipramine include lethality in overdose in patients with suicidal ideation; and anticholinergic effects in patients with constipation, narrow-angle glaucoma, or urinary hesitancy.[71] Clomipramine use is associated with the risk of QTc prolongation when used alone and in combination with other agents that prolong the QTc interval.[71,74] Clomipramine should also be used with caution in patients with a history of cardiovascular disease or conduction abnormalities. Because of sedative and anticholinergic side effects, clomipramine is not usually chosen as first-line therapy for older patients with OCD.[63] The use of antidepressants in older individuals is discussed in Chapter 88.

Dosage and Administration

Table 91-4 summarizes dosing guidelines for SSRIs and clomipramine. The SSRI dose to achieve response in OCD is often higher than doses used in other indications.[63,64] Data from fixed-dose studies in adults indicate that higher SSRI doses are more efficacious than lower doses, although there is a higher adverse effect burden.[27] However, there are no fixed dose studies to guide clinicians on how high to increase the clomipramine dose. If there is inadequate response to an average antidepressant dose, then it should be incrementally increased to the maximum dose within 5 to 9 weeks from the start of treatment. If there is an inadequate response after 4 to 6 weeks at the maximum dose, then another antidepressant should be tried.[63] Eight to 12 weeks is considered an adequate antidepressant trial for OCD treatment before changing to another agent.

TABLE 91-4

Adult Dosing of Serotonin Reuptake Inhibitors in the Treatment of OCD

Medication	Brand Name	Initial Dose	Usual Range	Comments
Citalopram[a]	Celexa	20 mg daily	20-40 mg daily	Maximum dose is 40 mg in adults daily to prevent QTc prolongation; maximum dose of 20 mg daily in older patients, CYP2C19 poor metabolizers, or use with concurrent moderate-to-strong CYP2C19 inhibitors (eg, cimetidine, omeprazole)
Clomipramine	Anafranil	25 mg daily	100-250 mg daily	Doses up to 300 mg daily may be needed in some patients. Steady-state trough plasma levels (clomipramine and desmethylclomipramine) should be <500 ng/mL (mcg/L; ~1.7 µmol/L) to minimize risk of conduction delays and seizures
Escitalopram[a]	Lexapro	10 mg daily	10-20 mg daily	Doses up to 40 mg may be needed in some patients
Fluoxetine	Prozac	20 mg daily	40-60 mg daily	Doses of 80 mg or higher may be needed in some patients
Fluvoxamine	• Luvox • Luvox CR	• 50 mg daily • 100 mg bedtime	• 100-300 mg daily • 100-300 mg daily	
Paroxetine	Paxil, Paxil CR, Pexeva	20 mg daily	40-60 mg daily	Higher doses may be needed in some patients
Sertraline	Zoloft	50 mg daily	50-200 mg daily	Higher doses may be needed in some patients

OCD, obsessive-compulsive disorder.

[a]Not FDA-approved for treatment of obsessive-compulsive disorder. Optimal dosing guidelines are not well established.

Data from References 12, 38, 40, 41, 71 and 75.

TABLE 91-5

Monitoring of Patients Being Treated for OCD

Medication	Adverse Medication Effects	Monitoring Consideration
Clomipramine	Dry mouth, constipation, nausea, dyspepsia, anorexia, somnolence, tremors, dizziness, nervousness	Assess at every visit, however, tolerance to these adverse events should occur in 2 weeks after treatment is started or a dosage increase is made. New onset adverse events may occur due to medication interactions
	Seizures	Assess if new onset seizures have occurred at each visit
	Orthostatic hypotension, tachycardia, ECG changes	Obtain baseline ECG and vital signs in pediatric patients, patients >40 years, those with cardiovascular disease, or those with other risk factors for QTc prolongation (eg, electrolyte abnormalities, concomitant QTc prolonging medications)
	Suicidality	Obtain at every visit. Highest risk is in patients ≤24 years
	Agranulocytosis, leukopenia	Obtain CBC with differential if patient complains of sore throat, fever
	Weight gain	Obtain vitals (including height and weight) and assess at each visit
SSRIs	Nausea, vomiting, diarrhea, sexual dysfunction, headache, insomnia	Should be assessed at every visit, but generally these adverse events and mild and short-lived. They may reoccur due to a new medication interaction
	Anxiety and agitation	Assess at each visit. May occur in some patients early in treatment
	Discontinuation syndrome	Slowly taper medication to reduce the occurrence of this adverse event. Patient education is key in recognizing its occurrence
	Suicidality	Assess at every visit. Highest risk is in patients ≤24 years
	QTc prolongation	Obtain baseline ECG and electrolytes. Of most concern with citalopram doses over 40 mg daily in adults and 20 mg daily in older patients or in those with risk factors >60 years old, female sex, cardiovascular disease, hypokalemia, hypomagnesemia, or concurrent use of medications or substances that prolong QTc

Alternative Medication Treatments

Augmentation with Antipsychotics

Augmentation of SSRI treatment with low-to-moderate doses of antipsychotics may be helpful,[12,27,76] and should be considered for patients with tic-related OCD, comorbid psychosis, and treatment-refractory symptoms. One-third of patients with treatment-refractory OCD respond to antipsychotic augmentation.[27] A recent meta-analysis found greater effect sizes for aripiprazole, haloperidol, and risperidone, whereas olanzapine,

paliperidone, and quetiapine failed to differentiate from placebo; however, quetiapine and olanzapine have been associated with at least one positive result from a randomized controlled trial.[77] First-generation antipsychotics, such as haloperidol, are less preferred given risk of extrapyramidal symptoms. As the long-term use of second-generation antipsychotic augmentation results in higher rates of adverse effects (eg, weight gain, increased blood glucose, lipid abnormalities), treatment should be discontinued if no benefits have been observed after 6 to 10 weeks.[27] Monitoring of antipsychotics can be found in Chapter 87.

Novel Augmentation Strategies

While augmentation with antipsychotics has the most evidence,[76] recent studies have examined novel augmentation approaches using glutamatergic agents (eg, *N*-acetylcysteine, lamotrigine, memantine, minocycline, riluzole, and topiramate) and ondansetron with initial promising results.[12,77] Some experts may prefer a trial of glutamatergic agents relative to antipsychotics to avoid antipsychotic-related adverse effects. Using D-cycloserine to augment ERP in patients with refractory OCD has had mixed results; further research is needed to identify patient and treatment characteristics that may differentially moderate response.[78]

Special Populations

Pregnancy

OCD may be triggered during the peripartum or postpartum period.[20] Risk–benefit analysis should be made by practitioners when deciding to use pharmacotherapy options during pregnancy.[63,79] The use of antidepressants in pregnancy and lactation is discussed in Chapter 88 and the use of antipsychotics in pregnancy and lactation is discussed in Chapter 87. Chapter 99 also discusses pregnancy and lactation in general.

Children and Adolescents

Younger patients exhibit poorer insight regarding obsessions, have more obsessions involving fear of harm and separation, and possess more rituals involving family members. Similar to adult OCD, CBT including ERP and family members and/or SSRI treatment are considered first-line for pediatric patients depending on illness and patient characteristics.[65,69,74] For mild-to-moderate pediatric OCD, CBT is superior to pharmacotherapy.[65]

Both childhood and adult OCD appear to respond similarly to antidepressant therapy with approximately at 50% response rate being seen during the initial SSRI trial in children. Clomipramine, fluvoxamine, sertraline, paroxetine, and fluoxetine are approved by the FDA for the treatment of OCD in children and adolescents.[63] Importantly, in children, the specific adverse effects of SSRI therapy more likely to occur compared to adults include treatment-emergent suicidal ideation, behavioral activation, and mania. In fact, all antidepressants now include a boxed warning regarding risk for suicide in patients 24 years and younger.[69,76] The risk of suicidality in youth is discussed in Chapter 88. Augmentation of SSRIs with antipsychotics or clomipramine is not well studied in pediatric patients but can be considered for treatment-refractory illness after failed SSRI augmentation with CBT, based on expert opinion and guideline recommendations.[69,74]

Antidepressant Dosing in Children

Pediatric patients often require smaller initial doses of medications (eg, fluoxetine 10 mg daily) compared to adults (eg, fluoxetine 20 mg daily). The starting dose of clomipramine in children is 25 mg daily in divided doses[71] with dose escalations occurring over the first 2 weeks up to 3 mg/kg or 100 mg, whichever is smaller. Over the next several weeks, the dose can be increased up to 3 mg/kg with a maximum of 200 mg daily given once daily at bedtime.

Choosing Pharmacotherapy

The choice of an SSRI for the treatment of OCD is based on history of prior response, safety, and adverse effect tolerability of the patient (see Table 91-5). While all SSRIs are considered equally efficacious, a patient may respond better to one agent over another.[63,66] Therefore, antidepressant treatment decisions should consider patient specific factors, such as previous treatment, family history of medication response, patient preference, and insurance coverage of medications. Currently, there are no guidelines that specifically address the use of pharmacogenomics testing in OCD.

However, there are data that can help guide medication selection based on specific gene medication pairs for many of the antidepressants used in treating OCD. A valuable resource for understanding dosing recommendations for these various medication and gene combinations is CPIC.[62] Use of these guidelines, along with any testing interpretation results, may help reduce the risk of antidepressant specific adverse events, potentially, facilitating successful treatment.

EVALUATION OF THERAPEUTIC OUTCOMES

Target symptoms of OCD should be monitored closely with degree of response being used to indicate a need to modify dosage, change medication, or augment therapy. Rating scales can be used to monitor symptom response to therapy for OCD (eg, Y-BOCS) and changes in QOL.[27,63] Response is often defined by an improvement of 25% to 35% in baseline symptoms, whereas remission is defined as a total Y-BOCS score less than 16 (out of a total score of 40), both of which still indicate substantial symptomatology.[27] The clinician should inquire about and address problematic adverse effects, including the emergence of suicidal ideation, reported by the patient, and the amount of time the patient spends obsessing and performing compulsions (see Table 91-5).[63] Additionally, changes in social and occupational functioning should be assessed.

10 After patients have responded in the acute phase of treatment, treatment gains are maintained with maintenance-phase strategies.[63] Monthly follow-up visits are recommended for at least 3 to 6 months, and a medication taper can be considered after 1 to 2 years of treatment depending on relapse prevalence, medication adverse effects, and patient preferences.[39,63,74] Treatment discontinuation results in higher relapse rates compared with treatment continuation[56] and medication should not be rapidly discontinued. Booster CBT sessions can reduce the risk of relapse when medication is withdrawn.[63] When making the decision to withdraw medication therapy, the dosage can be decreased by 10% to 25% every 1 to 2 months with careful observation for symptom relapse. However, most patients require lifelong medication therapy given chronicity of symptoms.[56]

CONCLUSION

Beginning with the *DSM-5*, both PTSD and OCD related disorders were removed from the anxiety disorder classification. Neurobiological changes in the HPA axis and the CSTC circuit are largely implicated in PTSD and OCD, respectively. The age of onset of PTSD is variable since it depends on trauma or stressful event exposure though it typically occurs before age 40 years while OCD has a bimodal age of onset peaking in late childhood/adolescence and in early adulthood. Both conditions have effective nonpharmacological methods to reduce symptoms including trauma focused therapy, EMDR for PTSD, and CBT with ERP in OCD. The SSRIs are first-line treatment for both conditions; however, moderate-to-high dose SSRIs are typically needed in OCD treatment. The use of antipsychotics in PTSD is controversial, whereas there is a clearer role for antipsychotic augmentation in OCD treatment. Pharmacotherapy should be continued for at least 1 year in PTSD and 1 to 2 years in OCD.

ABBREVIATIONS

5-HT	serotonin
ASD	acute stress disorder
CAPS	Clinician-Administered Posttraumatic Stress Disorder Scale
CBT	cognitive behavioral therapy
CPIC	Clinical Pharmacogenomics Implementation Consortium
CRF	corticotropin-releasing factor
CSTC	cortico-striatal-thalamo-cortical
CYP450	cytochrome P450 isoenzyme

DA	dopamine
dACC	dorsal anterior cingulate cortex
DBS	deep brain stimulation
EMDR	eye movement desensitization and reprocessing
ERP	exposure and response prevention
GABA	γ-aminobutyric acid
HPA	hypothalamic-pituitary-adrenal
MAOI	monoamine oxidase inhibitor
MRI	magnetic resonance imaging
NE	norepinephrine
NMDA	N-methyl-D-aspartate
NPY	neuropeptide Y
OCD	obsessive-compulsive disorder
PANDAS	pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection
PCL-5	PTSD Checklist for *DSM-5*
PET	positron emission tomography
PTSD	posttraumatic stress disorder
QOL	quality of life
SNP	single nucleotide polymorphism
SNRI	serotonin–norepinephrine reuptake inhibitor
SPECT	single-photon emission computed tomography
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TFCBT	trauma-focused cognitive behavioral therapy
TMS	transcranial magnetic stimulation
mPFC	medial prefrontal cortex

Y-BOCS	Yale-Brown Obsessive-Compulsive Scale

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SELF-ASSESSMENT QUESTIONS

1. Which of the following best describes the pathophysiology of posttraumatic stress disorder (PTSD)?
   A. Low concentrations of cortisol
   B. High levels of neuropeptide Y
   C. Underactive autonomic nervous system
   D. Decreased secretion of corticotropin-releasing factor
2. Which of the following is considered an intrusion symptom of PTSD?
   A. Irritability or anger outbursts
   B. Avoiding feelings about the trauma
   C. Recurrent disturbing dreams of the event
   D. Inability to recall an important aspect of the event

3. In order to meet the diagnostic criteria for acute stress disorder, symptom resolution occurs by what time period?

   A. 3 days

   B. 4 weeks

   C. 3 months

   D. 1 year

4. A 19-year-old college student was sexually assaulted at an off-campus party by an acquaintance 2 months ago. The patient presents to the outpatient clinic with complaints of difficulty falling and staying asleep, irritability, feeling numb, and being easily startled. Other reports include intrusive memories of the event, is missing at least 1 day of school a week, and avoids talking with family and friends about the event. You note on examination a restricted range of affect and nervousness and the patient refuses to talk about the details of the event. PTSD is diagnosed. What is the most appropriate first-line pharmacologic management of this patient?

   A. Paroxetine 10 mg every day

   B. Olanzapine 5 mg twice daily

   C. Diazepam 5 mg three times a day

   D. Amitriptyline 10 mg at bedtime

5. Which of the following agents has the most evidence to support its use as an augmenting agent in patients with PTSD who are on antidepressant therapy and continue to complain of impulsive anger?

   A. Prazosin

   B. Zolpidem

   C. Clonazepam

   D. Lamotrigine

6. A 41-year-old Marine veteran from the war in Afghanistan was diagnosed with PTSD 6 months ago. The patient has had a reduction in symptoms but continues to complain about memories of witnessing the deaths of three close friends during combat and Afghani children being gunned down by the Taliban. The patient continually blames themselves for the deaths of friends and is estranged from their partner. They are currently on sertraline 100 mg daily and has been on this dose for a month. What is the best recommendation at this time?

   A. Add quetiapine 25 mg daily

   B. Add phenelzine 15 mg at bedtime

   C. Increase sertraline to 150 mg daily

   D. Switch to venlafaxine extended-release 37.5 mg daily

7. Which of the following nonpharmacologic treatments is the most effective in the management of PTSD?

   A. Relaxation training

   B. Deep brain stimulation

   C. Electroconvulsive therapy

D. Trauma-focused cognitive behavioral therapy

8. A 29-year-old patient with PTSD is seen in the outpatient clinic for a follow-up appointment. The patient has been on venlafaxine extended-release 225 mg daily for the past 6 months, reports a 75% reduction in symptoms, and has returned to work as a schoolteacher. The patient asks how much longer they should remain on medication. Which of the following minimum durations of time should you discuss with the patient?

   A. 3 months

   B. 6 months

   C. 9 months

   D. 12 months

9. Results of neuroimaging studies suggest that there is a dysfunction in which of the following areas of the brain in patients with obsessive-compulsive disorder (OCD)?

   A. Nigrostriatal tract

   B. Hypothalamic pituitary axis

   C. Ventromedial prefrontal cortex

   D. Cortical-striatal-thalamic circuit

10. Which of the following is an example of a compulsion that a patient with OCD may report?

    A. Repeated thoughts of doubt

    B. Repetitive urges to place pens in a proper order

    C. Repeating the same verse from the bible silently

    D. Recurring thoughts of feeling contaminated after touching objects

11. A nurse practitioner would like to initiate paroxetine in a 20-year-old patient with OCD. Which of the following daily starting doses would you recommend?

    A. 20 mg

    B. 37.5 mg

    C. 50 mg

    D. 75 mg

12. An 11-year-old has been diagnosed with OCD. The patient's obsessions involve contamination and the patient's parent reports that the child showers three times a day and is constantly washing hands to the point of cracked and bleeding hands. This is beginning to interfere with the family's routines and the patient's ability to complete schoolwork and homework assignments. The parent requests that the patient be placed on medication. The patient is currently not taking any medications. Which of the following would be the most appropriate recommendation?

    A. Risperidone 1 mg 2 times daily

    B. Clomipramine 25 mg at bedtime

    C. Venlafaxine 25 mg 3 times daily

D. Fluoxetine 10 mg every morning

13. Which of the following is the most effective and least invasive nonpharmacological treatment for OCD?

A. Ablative neurosurgery

B. Deep brain stimulation

C. Exposure and response prevention

D. Trauma-focused cognitive behavioral therapy

14. A 32-year-old individual with a 10-year history of treatment refractory OCD complains of an increase in fears that his child will be hit by a tractor-trailer and die. This has led to the patient literally knocking on wood for up to 2 hours daily. The patient has been on escitalopram 20 mg daily for the past 3 years and lives in a rural area without access to psychotherapy. Which of the following would be the best augmenting agent to try?

A. Quetiapine

B. Haloperidol

C. Venlafaxine

D. Aripiprazole

15. A patient with newly diagnosed OCD has been on citalopram 20 mg daily for the past 3 months with a 50% reduction of symptoms based on the Yale-Brown Obsessive-Compulsive Disorder Scale. The patient inquires as to how much longer it is recommended that they stay on this medication. What is the most appropriate response?

A. 3 days

B. 9 weeks

C. 9 months

D. 3 years

16. Which of the following parameters should be obtained at baseline and checked at each visit in patients maintained on clomipramine 75 mg twice daily for OCD?

A. Weight

B. Blood glucose

C. Electrocardiogram

D. Complete blood count

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** There are many neuroendocrine and neurochemical abnormalities associated with PTSD. Patients with PTSD demonstrate hypersecretion of corticotropin-releasing factor but have subnormal levels of cortisol. Further, studies in nonmilitary patients have identified that lower plasma cortisol concentrations are associated with more severe PTSD symptoms.

2. **C.** Intrusion symptoms are characterized by distressing memories of the trauma. These can take the form of recurrent, distressing dreams or feeling that the trauma is reoccurring and may be associated with a similar physiologic reaction or psychological distress related to the trauma.

3. **B.** To meet diagnostic criteria for acute stress disorder (ASD), symptoms must last for at least 3 days and resolve within a month.

4. **A.** This patient meets diagnostic criteria for a diagnosis of PTSD, including significant impairment; therefore, pharmacotherapy is warranted. Antidepressants, including SSRIs and venlafaxine, are first-line treatment options in PTSD. Further, paroxetine is FDA-approved for the treatment of PTSD.

5. **D.** The addition of an antiseizure medication, such as lamotrigine or topiramate, to augment an antidepressant regimen is reasonable to target impulsive anger. Note: antiseizure medications should not be used as the sole therapeutic agent.

6. **C.** Optimization of the effective antidepressant medication, sertraline, in this case, and titration to an effective and well-tolerated dose should occur prior to augmenting with an additional medication. Further, due to the patient's positive response to sertraline thus far, it would not be appropriate to switch to another medication at this time.

7. **D.** Current guidelines emphasize the utility of trauma-focused cognitive behavioral therapy (TFCBT). Further, prolonged exposure individual trauma-focused psychotherapy in close proximity to the traumatic event resulted in lower rates of PTSD within 6 months. Data also support TFCBT is more effective than stress management or group therapy to reduce symptoms of PTSD.

8. **B.** Since this patient has responded well to venlafaxine extended-release, treatment should continue for at least another 6 months, for a total treatment duration of 1 year. Residual symptoms persist, strengthening the recommendation to continue treatment. With the patient's return to work, additional stressors may occur, further influencing the patient's response to treatment. Once an adequate treatment period has occurred, the medication should be slowly tapered to avoid withdrawal symptoms and reduce the risk for relapse.

9. **D.** Neuroimaging studies suggest that dysfunction in the cortical-striatal-thalamic circuits is responsible for impulsive behavior and inability to regulate socially acceptable behaviors. Drugs that decrease hyperactivity in the cortical-striatal-thalamic circuits decrease symptoms of OCD.

10. **C.** Obsessions are recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted, whereas compulsions are repetitive behaviors or mental acts that an individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.

11. **A.** Paroxetine 20 mg is the recommended starting dose for OCD treatment as exacerbation of anxiety in the early stages of OCD treatment is uncommon. A usual effective range for paroxetine is 20 to 60 mg daily. Doses of 80 mg or higher may be needed in some patients though they are above the FDA-approved max.

12. **D.** SSRIs are considered first-line treatment for both pediatric and adult OCD. Pediatric patients often require smaller initial doses of medications (eg, fluoxetine 10 mg daily) compared to adults (eg, fluoxetine 20 mg daily).

13. **C.** CBT with behavioral techniques (eg, exposure and response prevention [ERP]) is the most common initial nonpharmacologic treatment of choice in OCD. CBT with ERP is considered a first-line treatment option for both pediatric and adult OCD, especially in mild-to-moderate cases. It may be combined with pharmacologic treatment for moderate-to-severe cases of OCD. CBT is considered superior to pharmacologic interventions.

14. **D.** SSRI augmentation with antipsychotics is effective in one-third of patients with treatment refractory OCD. A recent meta-analysis found greater effect sizes for aripiprazole, haloperidol, and risperidone whereas olanzapine, paliperidone, and quetiapine failed to differentiate from placebo. In general, second-generation antipsychotics are preferred over first-generation antipsychotics for OCD treatment given less risk of extrapyramidal symptoms. Additionally, first-generation antipsychotic effectiveness for OCD treatment is mainly limited to patients with comorbid tics.

15. **C.** Medication taper can be considered after 1 to 2 years of treatment in patients with OCD.

16. **A.** Patient body weight should be assessed at baseline and at every office visit during clomipramine treatment because of its anticholinergic and antihistaminergic receptor activity. While clomipramine is associated with weight gain, it is not known to cause blood sugar abnormalities. Blood dyscrasias (eg, leukopenia, agranulocytosis) are rare so routine monitoring is unnecessary. ECG should be obtained at baseline in pediatric patients, those >40 years old, and those with cardiovascular disease. After obtaining a baseline ECG, follow-up assessments can be obtained as clinically indicated.