JAMA | Review

Obsessive-Compulsive Disorder
Advances in Diagnosis and Treatment

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IMPORTANCE Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder associated with significant impairment and a lifetime prevalence of 1% to 3%; however, it is often missed in primary care settings and frequently undertreated.

OBJECTIVE To review the most current data regarding screening, diagnosis, and treatment options for OCD.

EVIDENCE REVIEW We searched PubMed, EMBASE, and PsycINFO to identify randomized controlled trials (RCTs), meta-analyses, and systematic reviews that addressed screening and diagnostic and treatment approaches for OCD among adults (≥18 years), published between January 1, 2011, and September 30, 2016. We subsequently searched references of retrieved articles for additional reports. Meta-analyses and systematic reviews were prioritized; case series and reports were included only for interventions for which RCTs were not available.

FINDINGS Among 792 unique articles identified, 27 (11 RCTs, 11 systematic reviews or meta-analyses, and 5 reviews/guidelines) were selected for this review. The diagnosis of OCD was revised for the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, which addresses OCD separately from anxiety disorders and contains specifiers to delineate the presence of tics and degree of insight. Treatment advances include increasing evidence to support the efficacy of online-based dissemination of cognitive behavioral therapies, which have demonstrated clinically significant decreases in OCD symptoms when conducted by trained therapists. Current evidence continues to support the use of selective serotonin reuptake inhibitors as first-line pharmacologic interventions for OCD; however, more recent data support the adjunctive use of neuroleptics, deep-brain stimulation, and neurosurgical ablation for treatment-resistant OCD. Preliminary data suggest safety of other agents (eg, riluzole, ketamine, memantine, *N*-acetylcysteine, lamotrigine, celecoxib, ondansetron) either in combination with selective serotonin reuptake inhibitors or as monotherapy in the treatment of OCD, although their efficacy has not yet been established.

CONCLUSIONS AND RELEVANCE The dissemination of computer-based cognitive behavioral therapy and improved evidence supporting it represent a major advancement in treatment of OCD. Although cognitive behavioral therapy with or without selective serotonin reuptake inhibitors remains a preferred initial treatment strategy, increasing evidence that supports the safety and efficacy of neuroleptics and neuromodulatory approaches in treatment-resistant cases provides alternatives for patients whose condition does not respond to first-line interventions.

Supplemental content

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Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

JAMA. 2017;317(13):1358-1367. doi:10.1001/jama.2017.2200

Obsessive-compulsive disorder (OCD) is characterized by time-consuming, distressing, or impairing obsessions (repetitive unwanted thoughts, images, or urges) or compulsions (repetitive behaviors or thoughts), often accompanied by avoidance behaviors. The lifetime prevalence for OCD among adults in the United States is estimated to be 1% to 3%.[1,2] Age at onset of OCD is bimodal, with peaks in late childhood or early adolescence and again in early adulthood (ie, 20-29 years).[3] Although symptom trajectory is highly influenced by treatment, most patients experience a continuous symptom course, with up to a quarter exhibiting a waxing and waning pattern.[4] Individuals with OCD often have diminished quality of life, similar in magnitude to individuals with schizophrenia.[5] Substantial caregiver burden[6] and personal and societal economic costs are also associated with OCD; in 2004, OCD was associated with more disability-adjusted life-years (the number of years lost to disability) than multiple sclerosis and Parkinson disease combined.[7] Despite the burden of this disorder, it often goes unrecognized in both primary and psychiatric settings,[8-10] in part because its symptoms are often internally rather than externally manifested and patients may be reluctant to disclose thoughts or behaviors that they perceive as shameful or embarrassing. As a result, the mean time from OCD symptom onset to initial pharmacologic treatment is nearly 8 years.[11,12] Among patients who come to clinical attention, fewer than 40% receive OCD-specific therapy and fewer than 10% receive evidence-based treatment.[13]

The goals of this article are to review developments in the screening, assessment, diagnosis, and management of OCD in adults within the past 5 years. Recent advances include revision of the diagnostic criteria for OCD in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* and the forthcoming *International Classification of Diseases, 11th Revision*, both of which define hoarding disorder as a distinct diagnostic entity; improved quality and dissemination of computer-based psychotherapeutic treatments; improved evidence base for adjuvant pharmacologic treatments for treatment-refractory OCD; and emerging evidence for targeted neuromodulation.

Key Points

Question What advances in screening, diagnosis, and management of adult obsessive-compulsive disorder (OCD) have been introduced in the past 5 years?

Findings In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, OCD is now defined separately from anxiety disorders and there is an increased emphasis on the role of or relationships to comorbid tics, hoarding, and poor insight. There is growing support for novel dissemination methods for behavioral interventions (eg, online-based therapy), pharmacologic approaches (eg, neuroleptic augmentation of antidepressants), and neuromodulation (eg, deep-brain stimulation).

Meaning More accurate screening, precise diagnosis and formulation, and empirically supported treatments may lead to improved prognosis for adults with OCD.

Methods

We conducted a review of PubMed, EMBASE, and PsycINFO, using predefined search strategies. Search strings included the terms *obsessive compulsive disorder, assessment, screening, diagnosis, treatment,* and *management,* among others (see the eAppendix in the Supplement for search engine–specific search syntax and the eFigure for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] flow diagram). We limited our search to English-language reports pertaining to adults (≥18 years) between January 1, 2011, and September 30, 2016, and excluded opinion pieces and commentaries, focusing on randomized controlled trials (RCTs), meta-analyses, systematic reviews, and clinical practice guidelines. Two reviewers (M.E.H. and M.H.B.) decided which identified articles to include according to clinical importance and assessed the quality of evidence supporting therapeutic modalities, using the Grading of Recommendations Assessment, Development and Evaluation criteria.[14] Among 792 unique articles identified, we selected 27 (11 RCTs, 11 systematic reviews or meta-analyses, and 5 reviews/guidelines) to be highlighted in this review (eFigure in the Supplement). Seminal reports published before 2011 were included to provide foundational information and to contextualize more recent findings.

Results

Advances in Diagnosis

Like most psychiatric disorders, a diagnosis of OCD is based on clinical assessment rather than on laboratory or radiographic tests. Defining features of OCD include the presence of obsessions or compulsions that are time consuming (eg, >1 hour per day), are distressing, or impair daily function, and are not the direct result of a medical condition or substance use. Either obsessions or compulsions must be present, but not necessarily both to meet criteria for OCD.[15] **Table 1** describes common obsessions and corresponding compulsions in OCD. OCD is heterogeneous in presentation, and symptom profiles may vary widely between patients who meet diagnostic criteria. These symptoms are often accompanied by avoidance behaviors. Obsessions and compulsions must be differentiated from similar symptoms (eg, repetitive negative thoughts, delusions, perseverative thoughts) that are associated with other psychiatric disorders (**Table 2**). For instance, obsessions are characterized by distressing or upsetting repetitive intrusive thoughts, images, or urges, usually recognized as illogical by the patient. In contrast, repetitive negative thoughts often manifest as persistent worrying in depression (eg, in regard to relationships, financial difficulties) and rumination about past events in generalized anxiety (often taking the form of grief, guilt, or regret). Likewise, compulsions are repetitive behaviors or thoughts performed to address anxiety or distress associated with obsessions and must be differentiated from stereotypies and habits (Table 2). Ancillary symptoms include anxiety related to the obsessions or in response to not being allowed to perform compulsions, and avoidance of situations or behaviors that may trigger obsessions or compulsions.[16]

The *DSM-5*, published in 2013, includes several clinically relevant changes from previous versions of the *DSM*, namely, removal of OCD from anxiety disorders and placement in a new category called obsessive-compulsive and related disorders; removal of the requirement that individuals have insight into their obsessions, that is, recognizing that they are a "product of his or her own mind," and the addition of a specifier to distinguish among good or fair, poor, and absent insight or delusional beliefs; addition of a co-occurring current or past tic disorder as a specifier; and addition of hoarding disorder as a new, separate diagnosis.[17] The choice to move OCD into

Table 1. Common Obsessions and Corresponding Compulsions in Obsessive-Compulsive Disorder

Obsessions[a]	Specific Examples	Compulsions [b]	Specific Examples
Fear of contamination[c]	Preoccupation or disgust with bodily waste; repetitive concern of spreading illness	Cleaning or washing	Excessive hand washing or cleaning of household items (long after they are reasonably clean)
Persistent doubting	Anxiety that the house door is unlocked despite having just locked it, or that the oven is turned off despite having just turned it off	Checking	Repeatedly checking that oven is off, doors are locked; driving back along a road to ensure that no one was injured; excessively checking writing to ensure no error was made
Violent or sexual intrusive thoughts	Intrusive, unwanted violent or horrific images; unwanted sexual images of strangers, family, friends	Repetitive "undoing" thoughts	Repeated, "neutralizing" thoughts (eg, "I am not a violent person," repeated asking for reassurance that one did not commit a violent or unwanted sexual act)
Fears of causing harm	Intrusive fears of dropping an infant one is holding; fear of inadvertently hitting pedestrians when driving	Repeated behaviors, checking	Repeatedly driving past crosswalks to check for injured pedestrians
Symmetry	Excessive worry and distress if items on a bookshelf are not arranged symmetrically	Ordering or arranging	Repeatedly arranging books on a bookshelf so that the spines are exactly aligned
Religious scrupulosity	Excessive concern with "right vs wrong"	Religious compulsions	Excessive prayer or apologies to God; need to tell or confess
Superstitions	"Lucky" or "unlucky" numbers or colors	Superstitious behaviors	Avoiding writing unlucky numbers; repeating activities a certain "lucky" or "right" number of times

[a] Obsessions are unwanted, repetitive thoughts.

[b] Compulsions are repetitive behaviors or thoughts. Often, but not always, performed to address anxiety associated with obsessions. Avoidance behaviors are also common in response to many obsessions. For example, an individual with an obsessive fear of dropping infants may avoid interacting with children altogether.

[c] Individuals with contamination fears may not use public bathrooms or public transportation.

its own category was based on phenotypic, neuroimaging, genetic, and treatment-response data that strongly suggest that although they share many features with other anxiety disorders, anxiety is not a core component of OCD and related disorders but is rather a secondary manifestation.[18,19] Not all individuals with OCD experience anxiety; many instead report only interference in daily activities or avoidance behavior.[20]

The addition of an insight specifier broadens the diagnosis to include individuals with little to no insight into their obsessions, which may be more likely to capture individuals with comorbid psychosis. This is clinically relevant, given the recently documented high rates of comorbidity between psychotic-spectrum disorders (eg, schizophrenia) and OCD.[21] In addition, poor insight can be associated with increased obsessive-compulsive severity, hoarding symptoms, and unemployment.[22] The tic-related specifier was added, in part, in light of evidence that individuals with tic disorders may have differential responses to treatment and because of evidence that OCD with tics may have a different genetic architecture than OCD without them.[23] There is emerging evidence that individuals with OCD and a co-occurring tic disorder are more likely than those without one to experience obsessive-compulsive symptom relief from neuroleptic augmentation (eg, haloperidol, risperidone).[24] Last, hoarding disorder is now recognized as a separate diagnostic entity, given that the majority of individuals with hoarding do not meet diagnostic criteria for OCD and factor analytic studies consistently reveal that hoarding symptoms segregate from other OCD symptoms. Furthermore, hoarding symptoms in OCD appear less responsive to typical OCD treatment and may improve with hoarding-specific therapies.[25]

Because of OCD's relatively low prevalence and frequent comorbidity with more commonly occurring comorbid psychiatric conditions (eg, depression), screening for it does not routinely occur in primary care settings[9]; however, a clinician may be prompted to ask about OCD symptoms according to patient report or exhibited behaviors (eg, repetitive behaviors) or physical signs of OCD (eg, chapped hands because of excessive washing). To further assess for symptoms that may indicate the presence of OCD, the clinician may ask the patient about the presence of repeated cleaning; repeated, unwanted, and illogical thoughts; or checking or counting behaviors.[26] When OCD is suspected, useful approaches include inquiring in more detail about the symptoms noted or observed (eg, onset, time spent engaging in obsessions or compulsions, associated distress or impairment) or administering a brief screening tool.

Recent reviews have detailed well-validated screening tools that are appropriate for the primary care setting.[27,28] Among these, the semistructured, clinician-administered Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)[29,30] is considered the gold standard for assessment of OCD symptoms and severity, given its good reliability, internal construct validity, and wide use in clinical research. The Y-BOCS assesses the presence of 64 obsessions and compulsions as well as associated symptom severity. However, the scale is long in comparison to most behavioral screening tools used in primary care, and its administration requires trained raters. These attributes may limit its widespread use in primary care settings.

Several brief self-rating forms are available, many of which are sensitive to symptom changes with treatment. One example is the Obsessive-Compulsive Inventory, Short Version (OCI-SV),[31] which typically requires 5 minutes to complete, demonstrates moderate convergence with the Y-BOCS, and consists of 18 items (each rated 0 to 4, according to degree of associated distress). Scores greater than or equal to 21 (out of 72) on the OCI-SV suggest the presence of OCD. An alternate short survey, the Florida Obsessive Compulsive Inventory, based on the Y-BOCS in structure and content, consists of a 20-item symptom checklist and a 5-item severity scale. Like the Obsessive-Compulsive Inventory, Short Version, the Florida Obsessive Compulsive Inventory demonstrates strong reliability and convergence with Y-BOCS scores, as well as treatment sensitivity.[32]

Advances in Treatment

Substantial evidence supports the use of cognitive behavioral approaches and selective serotonin reuptake inhibitors (SSRIs) in the treatment of OCD. Most patients will experience at least some symptom relief with these interventions either alone or in combination.[33] Given the proven efficacy of SSRIs and cognitive behavioral therapy (CBT), they are often used together in clinical practice.[34] However,

Table 2. Differential Diagnosis of Obsessive-Compulsive Disorder in Adults

	OCD	OCPD	GAD	Social Anxiety	MDD	Grooming Disorders	Psychotic Disorders	ASD	Eating Disorders	BDD	Tourette Syndrome or Chronic Tic Disorder
Thoughts											
Recurrent, unwanted, distressing thoughts (eg, words, sounds, or phrases)	✓								✓		
Thoughts concerning an anxiety-inducing topic, often about past events			✓	✓	✓				✓	✓	
Persistent thoughts about a given topic, often pleasurable (eg, repeated or fixed focus on a particular interest)		✓	✓					✓			
A fixed, false belief that is resistant to fact	[a]						✓			✓	
Behaviors											
Repetitive actions (physical or mental), often performed to neutralize anxiety. Done consciously with intent, although can become habitualized.	✓					✓		✓	[b]	[b]	
Repeated, unnecessary assessment (eg, that the stove is in the "off" position)	✓	✓	✓			✓					
Involuntary movement or vocalization, oftentimes brief, repetitive, and stereotyped. Wax and wane in type and intensity.											✓
Repeated, often semiconscious behaviors that can be stopped when brought to attention, but recur when distracted (eg, nail biting, tapping)						✓					
Repetitive movement, posture, or utterance (eg, flapping hands). Does not wax and wane; occurs with anxiety or engagement in another activity.								✓			
Action taken to avert contact with feared stimulus (either in thought or external environment)	✓		✓	✓	✓				✓		

Abbreviations: ASD, autism spectrum disorder; BDD, body dysmorphic disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; OCPD, obsessive-compulsive personality disorder.

[a] Patients with OCD with poor insight may exhibit delusions.

[b] Patients with eating disorders or BDD may also engage in repeated checking of weight or a particular body part to avoid anxiety.

even after adequate treatment trials, 40% to 60% of patients endorse residual, impairing symptoms after initial treatment,[35] prompting the investigation of augmentation strategies, novel pharmacologic agents, and neuromodulatory approaches.

Psychological Interventions

Cognitive behavioral therapy is the most effective evidence-based psychotherapy for OCD and, when performed by experienced practitioners, may also be the most effective treatment of any type, including pharmacotherapy.[36-40] It has demonstrated effectiveness in both individual and group settings[41] and involves 2 components: cognitive reappraisal or restructuring (the *C* in CBT) and behavioral interventions (the *B*), typically in the form of exposure-response prevention. The 2 components of CBT can be used either jointly or independently, although in practice, exposure-response prevention is the most frequently used approach.[39,40] Exposure-response prevention for OCD is a structured, manualized psychotherapy that involves exposing the patient to stimuli to provoke obsessions and the accompanying anxiety and distress, and instructing the patient to inhibit the associated compulsions or avoidance behaviors ("response prevention"). More cognitively based CBT modalities that focus on reappraisal and restructuring of maladaptive cognitions have also demonstrated short- and long-term improvements in OCD symptom severity; however, there is no evidence that adding cognitive elements to exposure-response prevention improves efficacy.[42] Nonetheless, cognitively based modalities may be preferred among patients who lack insight into their obsessions or are not able to tolerate in vivo exposure to feared stimuli.

Table 3. First-Line Behavioral and Pharmacologic Treatment Options for Obsessive-Compulsive Disorder in Adults[a]

Modality	Description	Frequency and Duration	SMD (95% CI)	NNT (95% CI)
Psychotherapy				
Exposure-response prevention	Controlled, repeated, and prolonged exposure to obsession-triggering stimuli with instructions to avoid compulsive behavior	13-20 weekly sessions or weekday daily sessions for 3 wk; periodic "booster" sessions may be offered within 3-6 mo after initial treatment	1.33 (0.91-2.57)[b,40]	3 (2-5)[b,40]
Cognitive therapy	Identifying maladaptive/illogical beliefs about obsessions that drive behavior (eg, compulsions) and developing more useful schemas to counter erroneous appraisals/valuation of obsessions			
Medication				
	Starting Dose, mg/d	**Target Dose, mg/d**		
SSRIs[c]				
Fluoxetine	20	80	0.61 (0.44-0.92)[d,e,44]	5 (3-8)[d,f,44]
Fluvoxamine	50	300		
Sertraline	50	200		
Paroxetine	20	60		
Citalopram	20	40[g]		
Escitalopram	10	40		
Tricyclic				
Clomipramine	25	250[h]	0.95 (0.68-1.25)[i,45]	

Abbreviations: NNT, number needed to treat; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor.

[a] The treatment modalities described are associated with an "A" Grading of Recommendations Assessment, Development and Evaluation level of evidence. The references represent systematic reviews or meta-analyses.

[b] Comparators consisted of unblinded control conditions (n = 37 trials). There is insufficient evidence to support the superiority of cognitive therapy vs exposure-response prevention.

[c] Assess adequate response to SSRI therapy 8-12 weeks after initiation, with 4-6 weeks at maximal tolerable dose.[36,37] There is insufficient evidence to support the superiority of any particular SSRI over any other. All appear to have similar efficacies.

[d] Comparators consisted of blinded, placebo-control conditions (n = 17 trials).

[e] Assuming SD = 8.65 for the Yale-Brown Obsessive-Compulsive Scale.

[f] NNT may differ by dose.

[g] The Food and Drug Administration has issued a recommendation not to exceed a daily dose of 40 mg because of increased risk of QT-segment prolongation, and not to exceed 20 mg among certain populations (eg, >60 years, coadministration of cytochrome P450 2C19 inhibitors such as cimetidine).[46]

[h] Trough (≥12 h postdose) combined serum concentration of clomipramine and desmethylclomipramine should remain <500 ng/mL to reduce risk of seizure and cardiac-conduction delay.

[i] Comparators consisted of blinded, placebo-controlled conditions (n = 7 trials), fluvoxamine (n = 1 trial), and desipramine (n = 1 trial). There is insufficient evidence to support the superiority of clomipramine vs any of the SSRIs.

However, there are some barriers to CBT treatment, including lack of availability (eg, few local clinicians, especially those trained in OCD-specific approaches; high out-of-pocket costs), intense time requirements (typically 1 or more hours a week for therapy sessions, plus daily "homework" assignments during at least 12 weeks), and patient motivation to engage in CBT. Recent research has focused on improving dissemination of CBT with technology- or Internet-based delivery. Evidence from a meta-analysis suggests that remote CBT (via an online platform) demonstrates efficacy similar to that of in-person treatment.[43]

Pharmacologic Interventions

Selective Serotonin Reuptake Inhibitors | Selective serotonin reuptake inhibitors compose first-line pharmacologic treatment for OCD, given their documented efficacy in reducing OCD symptoms and demonstrated tolerability across multiple trials.[36,37] Meta-analyses of blinded placebo-controlled head-to-head trials have failed to demonstrate meaningful differences in efficacy between specific SSRIs, however, which suggests that despite labeling differences, all SSRIs may be equally effective in treating OCD.[33,44] When likelihood of treatment response is examined (typically defined as a decrease of 25% to 35% in OCD severity), SSRIs have a number needed to treat of 5 (95% CI, 3 to 8) compared with placebo.[44] Clinical practice guidelines suggest that optimal treatment for OCD involves using SSRIs at the maximal tolerated dose within the Food and Drug Administration dosing guidelines (**Table 3**) for at least 8 to 12 weeks.[36,37] Higher doses of SSRIs have been demonstrated to be modestly (but significantly) more effective than lower ones in treating OCD.[47] Although up to 12 weeks is often needed to determine responsiveness to SSRI pharmacotherapy, the treatment response curve follows a logarithmic shape, with the greatest incremental benefits occurring by week 6, on average.[48] Further research is needed to determine the prognostic utility of early SSRI response or nonresponse, as well as the likelihood and trajectory of delayed treatment response with SSRIs. Given the greater adverse effect profile and the absence of evidence suggesting differences in efficacy between SSRIs, at least 8 to 12 weeks of treatment is suggested before determination that a particular SSRI is not beneficial. In addition, evidence from meta-analyses suggests that as many as 25% of patients with treatment-refractory OCD may benefit from SSRI monotherapy up to 28 weeks after initiation.[49,50] Further evidence suggests that continuing SSRI medications for at least 6 to 12 months after response to treatment is advisable; withdrawing SSRIs at any point is likely associated with a significant risk of relapse. Placebo-controlled discontinuation studies suggest that more than half of OCD patients who experience a response to SSRI will experience a relapse in OCD symptoms within the next 6 months (number needed to harm = 4 compared with continued SSRI monotherapy).[51-53]

Table 4. Clinical Characteristics Associated With Obsessive-Compulsive Disorder (OCD) Treatment Response

Characteristic	Implications for Treatment	
	Psychotherapy	Pharmacotherapy
Tics[55]	Habit-reversal techniques (involving identifying and prioritizing tics, monitoring premonitory urges to tic, and developing competing, intentional behaviors) and relaxation training are often used in conjunction with exposure-response prevention to address tics	Some evidence to suggest decreased efficacy of SSRIs (specifically, fluoxetine) in individuals with comorbid tics. SSRI augmentation with atypical neuroleptics (eg, risperidone, quetiapine) is equally effective in individuals with or without tics. Augmentation with haloperidol may be more effective in individuals who are treatment refractory to fluvoxamine with comorbid tics compared with those without tics.
Hoarding[25]	Decreased efficacy of exposure-response prevention and CBT; hoarding-specific individual or group CBT indicated for motivated patients	Generally decreased efficacy of first-line pharmacologic treatments; limited or no evidence to support second-line treatments (eg, atypical antipsychotic augmentation)
Poor insight[22]	Decreased motivation for initiation and compliance with treatment	Decreased efficacy of first-line pharmacologic and cognitive behavioral interventions; more likely to require multiple, sequential SSRI trials

Abbreviations: CBT, cognitive behavioral therapy; SSRI, selective serotonin reuptake inhibitor.

Nearly 50 years ago, clomipramine, a serotonin-selective tricyclic antidepressant, was the first medication demonstrated to be effective for OCD, and it is still used today. It remains the gold standard for treatment; however, it is unclear whether clomipramine is actually more effective than SSRIs in treating OCD. Some meta-analyses of RCTs have demonstrated larger treatment-effect sizes for clomipramine than for SSRIs.[45] A recent meta-analysis demonstrated similar effect sizes for both clomipramine and SSRIs when publication year and other characteristics of the underlying population were adjusted for.[33] However, in practice SSRIs are typically preferred as first-line agents because of their greater tolerability. Specifically, clomipramine has substantial anticholinergic effects, such as dry mouth, blurred vision, constipation, fatigue, tremor, and hyperhidrosis, that are minimal or absent with SSRI treatment. Furthermore, clomipramine is associated with increased risk of arrhythmia and seizures at doses greater than 200 mg daily, thus requiring monitoring of serum concentration. Although SSRI therapy carries the risk of serotonin syndrome, this adverse effect is uncommon and rarely leads to fatality, even in overdose.[54] Thus, clomipramine is most appropriate as a second-line treatment for patients who do not respond to SSRIs. It is also sometimes used at low doses as an augmentation strategy to SSRI pharmacotherapy, although this treatment strategy has never been studied in a controlled clinical trial, to our knowledge.

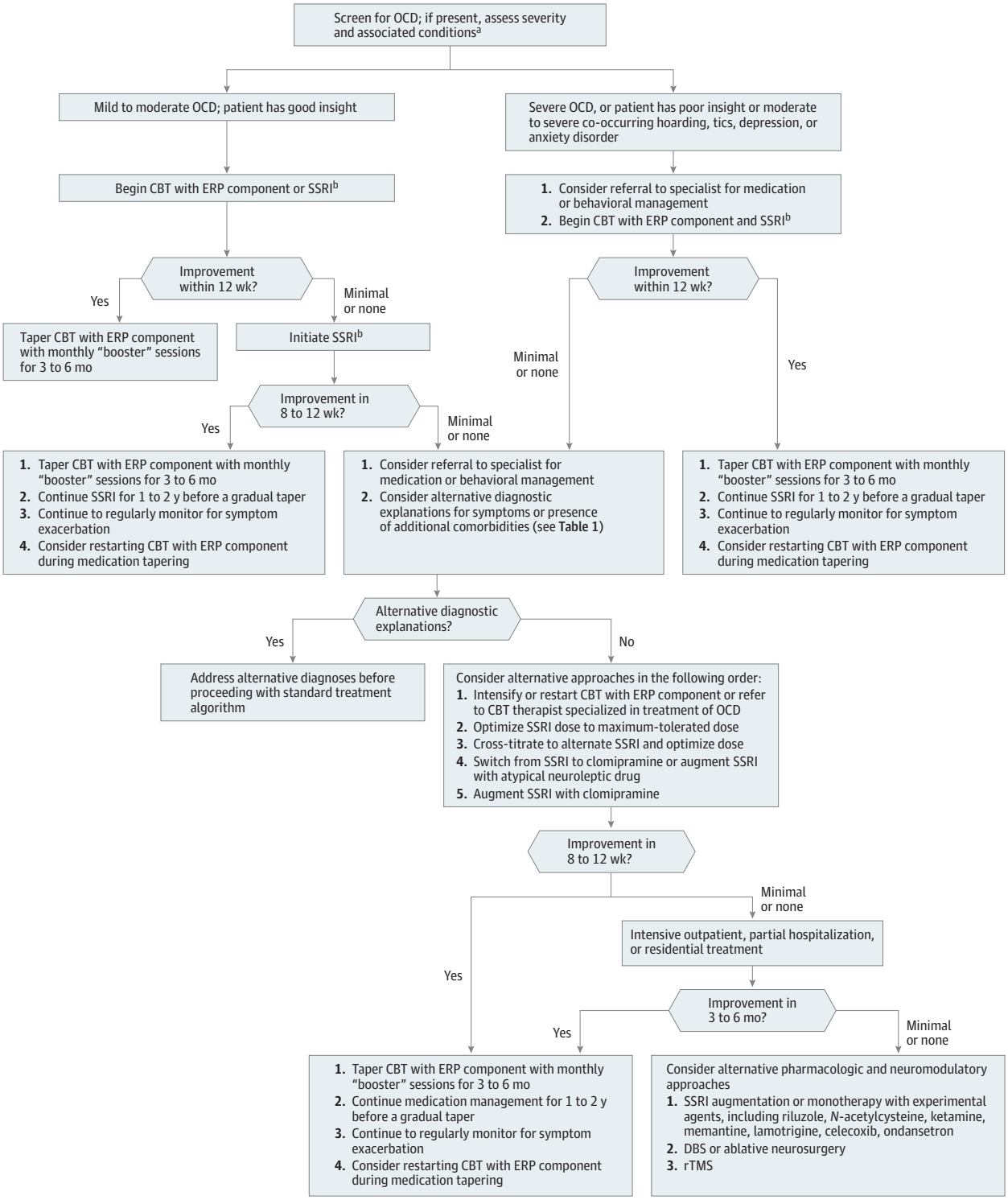
Augmentation Strategies for Treatment-Nonresponsive OCD | Approximately a quarter of OCD patients do not achieve a treatment response (typically defined as a greater than 25%-35% reduction in OCD severity or "very much" or "much improved" on the Clinical Global Impressions scale) after SSRI pharmacotherapy or CBT. Moreover, a 35% reduction in symptoms suggests that most treatment responders continue to experience significant OCD symptoms.[35] In addition, specific patient characteristics may be associated with unique patterns of treatment response (**Table 4**). Therefore, a rational approach to treating ongoing or residual symptoms after initial treatment is needed (**Figure**). When a patient fails to achieve adequate symptom relief on a trial of an SSRI, CBT, or their combination, reasonable options include switching to a different SSRI or clomipramine, or augmentation with additional medications.[36,37] Addition of neuroleptic agents (also commonly called antipsychotics) is one of the most commonly used augmentation strategies. Meta-analysis from RCTs demonstrates the effectiveness of neuroleptic augmentation of SSRIs for treatment-refractory OCD (number needed to treat = 5; 95% CI, 3 to 8).[24,50] There do not appear to be differences in efficacy between neuroleptics, either typical or atypical, although this type of augmentation may be particularly effective in reducing OCD symptoms in patients with comorbid tics (number needed to treat = 2; 95% CI, 1 to 5).[50] Given that neuroleptic augmentation is effective in approximately 30% of treatment-refractory OCD patients and that these medications carry a significant adverse effect burden, including weight gain and increased risk of diabetes, if clear symptom improvement is not observed after 6 to 10 weeks of treatment, neuroleptic augmentation should be discontinued.

Although appropriately viewed as a first-line treatment for OCD, CBT is also very effective in OCD patients judged refractory to pharmacotherapy. Specifically, a recent study demonstrated that individuals with SSRI-refractory OCD who were randomized to CBT demonstrated more significant treatment gains than those randomized to risperidone or placebo.[56] For severe treatment-refractory symptoms, intensive residential or inpatient treatment may be beneficial, although the long-term efficacy and cost-effectiveness of these approaches are largely unknown.[57]

There are also several promising pharmacologic augmentation strategies for treatment-resistant OCD whose efficacy has not yet been clearly demonstrated. In particular, specific agents with adequate safety profiles and preliminary evidence of OCD symptom reduction in open-label or small RCTs include ketamine,[58,59] riluzole,[60,61] *N*-acetylcysteine,[62] memantine,[63] lamotrigine,[64] celecoxib,[65] and ondansetron.[66] There is also interest in the use of nutraceuticals such as myoinositol, glycine, milk thistle, and serotonin (5-hydroxytrypophan),[67] although there is insufficient evidence to support the routine use of any of these agents in treating OCD.

Benzodiazepines, which are effective for the short-term treatment of anxiety disorders,[68] have limited efficacy in OCD. Clinical trials have not demonstrated a benefit of concomitant benzodiazepine use and SSRI pharmacotherapy for OCD, and available evidence does not support their long-term benefit for improving OCD symptoms compared with placebo.[69,70] Benzodiazepines are commonly used early in treatment to acutely control distressing anxiety and insomnia before the benefits of SSRI pharmacotherapy or CBT take effect.[71] However, given the significant risk of physiologic dependence and lack of clear long-term benefit, benzodiazepines should be used with restraint and for limited duration in OCD.

Figure. Suggested Treatment Algorithm for Obsessive-Compulsive Disorder in Adults



CBT indicates cognitive behavioral therapy; DBS, deep-brain stimulation; ERP, exposure-response prevention; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitor; rTMS, repetitive transcranial magnetic stimulation; SSRI, selective serotonin reuptake inhibitor.

[a] Severity of OCD as determined by Obsessive-Compulsive Inventory, Short Version (OCI-R) scores: mild (scores of 15-19), moderate (20-34), and severe (≥35). If OCD is suspected according to OCI-R score or clinical history, the Yale-Brown Obsessive-Compulsive Scale may be administered for further assessment of obsessive-compulsive and associated symptoms.

[b] There is insufficient evidence to support the superiority of one particular SSRI over any other; all appear to have similar efficacies.

Emerging Neuromodulation Therapies

Neurosurgical techniques, focused on lesioning specific components of the neural circuitry implicated in OCD, have been used for decades in treatment of adults with severe, treatment-refractory symptoms. Abnormalities in corticostriatal-thalamic-cortical circuits connecting orbitofrontal cortex, anterior cingulate, basal ganglia, and thalamus are hypothesized to be central to OCD pathophysiology and have been consistently implicated in neuroimaging studies.[72] Ablative procedures commonly practiced for treatment-refractory OCD include anterior cingulotomy, capsulotomy, subcaudate tractotomy, and limbic leucotomy (a combination of anterior cingulotomy and capsulotomy). The specifics of each procedure are covered elsewhere.[73] Reviews of open-label studies of these neurosurgical procedures in OCD suggest 50% to 60% response rates observed after 6 to 24 months.[74] However, given the invasive nature of any neurosurgical approach and limited evidence base in OCD (in comparison to behavioral and SSRI therapy), it should be reserved for only the most severe, treatment-refractory cases.

Deep-brain stimulation, which was initially piloted for the relief of movement disorders such as those found in Parkinson disease and has since expanded to include neuropsychiatric disorders, involves the surgical implantation of electrodes and the introduction of targeted electrical stimulation to specific brain regions. Deep-brain stimulation for OCD typically targets the anterior limb of the internal capsule/nucleus accumbens or thalamus/subthalamic nucleus.[75] Crossover trials comparing OCD symptomatology and severity when the implanted electrodes are on compared with when they are off demonstrate the efficacy of deep-brain stimulation for both brain regions,[75] and recent studies have further refined the brain regions of interest, improving treatment outcomes.[76] A meta-analysis of 31 studies involving 116 participants with OCD who underwent deep-brain stimulation estimated a 45.1% decrease in post-treatment Y-BOCS total score and a 60.0% response rate (defined as >35% reduction in post-treatment Y-BOCS score).[75] Although nonsurgical neuromodulation techniques, such as electroconvulsive therapy and repetitive transcranial magnetic stimulation, both of which have demonstrated efficacy in specific mood disorders, have been investigated in the treatment of OCD, the current body of evidence is too limited to comment meaningfully on their effectiveness in OCD.[77,78] The eTable in Supplement summarizes options for approaching treatment-refractory OCD.

Discussion

Despite the severe impairment and burden of OCD, it often goes unrecognized and undertreated or untreated. Primary care clinicians should be vigilant in recognizing OCD symptoms in their patients and initiating appropriate pharmacologic treatment or referrals for treatment. Conditions that can commonly be confused with OCD, such as generalized anxiety disorder, should be considered and ruled out. Important moderators of treatment efficacy (eg, presence of comorbid tics or hoarding symptoms, level of insight) should also be assessed because these may help guide choice of initial treatment (Table 4)

CBT still has the strongest evidence base and, when available, should be first-line treatment for OCD. Recent advances have been made in the dissemination of CBT through online platforms and in group settings. SSRIs are the only class of medications with documented efficacy as a primary agent and are generally well tolerated. Neuroleptic augmentation of SSRIs is an effective approach for patients who do not respond to first-line treatments for OCD, whereas for severe treatment-refractory OCD, neurosurgery and deep-brain stimulation are possible options. Finally, several emerging treatments may prove beneficial for OCD and warrant further study, although these options are best considered in collaboration with or by referral to a clinician with expertise in OCD treatment. Treatment response can be closely monitored at regular intervals with validated self-report instruments (such as the OCI-SV).

Limitations

Our review is limited by multiple factors. First, we focused on work published in the past 5 years and therefore may have excluded advances before 2011. Second, because we primarily addressed recent advances, foundational diagnostic and treatment topics received only brief mention; readers are directed to the American Psychiatric Association guidelines for detailed recommendations.[36,37] Third, because the majority of studies involving novel pharmacologic agents and neuromodulation techniques consist of open-label trials or RCTs of brief follow-up duration and limited sample size, we cannot provide specific recommendations in regard to these treatment approaches. Fourth, good predictors of treatment response are still lacking, although this is an active area of investigation.

Consensus Guidelines

The American Psychiatric Association practice guideline (published in 2007[37] and selectively updated in 2013[36]) and the Anxiety and Depression Association of America *Clinical Practice Review for OCD* (2015)[79] are largely in concordance with this review, including general screening and diagnostic techniques, first-line behavior and pharmacologic approaches, and the exploratory nature of novel pharmacologic agents and neuromodulation modalities.

Conclusions

The dissemination of computer-based CBT and improved evidence supporting it represent a major advancement in treatment. Although CBT with or without SSRIs remains a preferred initial treatment strategy, increasing evidence that supports the safety and efficacy of neuroleptics and neuromodulatory approaches in treatment-resistant cases provides alternatives for patients who fail to respond to first-line interventions.

ARTICLE INFORMATION

Author Contributions: Drs Hirschtritt and Bloch had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Hirschtritt, Bloch.
Drafting of the manuscript: Hirschtritt, Bloch.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bloch.
Supervision: Bloch, Mathews.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Bloch reports receiving grant or research support from the National Institutes of Health (NIH), Tourette Association of America, the Brain & Behavior Research Foundation, and the Patterson

Foundation. He reports serving as a consultant to Therapix Biosciences and Biohaven Pharmaceuticals. Dr Mathews reports receiving research support, honoraria, and travel support from the Tourette Association of America and is the cochair of the group's scientific advisory board. She has also received grants from the NIH and the Patient-Centered Outcomes Research Institute. No other disclosures were reported.

Funding/Support: Dr Bloch acknowledges the support of the Tourette Syndrome Association of America, the Brain & Behavior Research Foundation, the Patterson Foundation, and the State of Connecticut, Department of Mental Health and Addiction Services.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: This publication does not express the views of the Department of Mental Health and Addiction Services or the State of Connecticut. The views and opinions expressed are those of the authors.

Additional Contributions: We appreciate the assistance of Evans M. Whitaker, MD, MLIS (University of California, San Francisco, Medical Library), in developing the systematic search strategy used in this report. Dr Whitaker did not accept any financial compensation for his contributions to this article.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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