GUIDELINE WATCH (MARCH 2013): PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER

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This watch summarizes new evidence and developments since the 2007 publication of the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Obsessive-Compulsive Disorder*. The authors of this watch participated in the work group that developed the 2007 guideline (American Psychiatric Association 2007).

We find that the guideline remains substantially correct and current in its recommendations. Some recommendations are now supported by stronger evidence, and more data are available regarding rates of response to some interventions. In addition, new rating scales have been developed, and preliminary studies suggest additional treatments or modes of delivery that deserve further study. This watch focuses on controlled trials, systematic reviews, and meta-analyses but also considers data from small case series or uncontrolled observations. Only those sections of the 2007 guideline for which new treatment-related information is available are covered. This guideline is focused on the treatment of adults only and does not cover the treatment of children and adolescents with obsessive-compulsive disorder (OCD).

During development and approval of this watch, from May 2012 to January 2013, Dr. Koran reports receiving income for work as a member of the Speakers Bureau for Forest Pharmaceuticals and as a consultant to F. Hoffman-La Roche Ltd. He received royalties from Cambridge University Press and has the potential to receive royalties from UpToDate, Inc. Dr. Simpson received medication at no cost from Janssen Pharmaceuticals for a clinical trial funded by the National Institute of Mental Health, received research support to participate in a multisite clinical trial sponsored by Transcept Pharmaceuticals, provided a 1-hour consultation to Quintiles, Inc., on therapeutic needs for patients with obsessive-compulsive disorder (OCD), and received royalties from Cambridge University Press and UpToDate, Inc.

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Guideline watches summarize significant developments in practice that have occurred since publication of an APA practice guideline. Watches may be authored and reviewed by experts associated with the original guideline development effort and are approved for publication by APA's Executive Committee on Practice Guidelines. Thus, watches represent the opinion of the authors and approval of the Executive Committee, but not APA policy.

METHODS

The systematic literature search for the 2007 guideline ended in 2004, although some publications from 2005 were included. For this guideline watch, we searched the Cochrane database and MEDLINE, using PubMed, for randomized, controlled trials, meta-analyses, and other articles published in English since December 2004. In PubMed, we searched the MeSH terms "obsessive-compulsive disorder," "obsessive behavior," and "compulsive behavior" as well as the following title and abstract words or phrases: "checking behavior," "checking behaviors," "compulsion," "compulsions," "compulsive," "hoarding," "obsession," "obsessional," "obsessions," "obsessive," and "rituals." Titles, abstracts, and keywords in the Cochrane database were searched for the words "obsessive," "obsessional," "compulsive," "compulsion," and "ritual." After duplicate citations were eliminated, these search strategies yielded 958 articles, which were screened by two separate raters for relevance to OCD treatment: 722 articles were excluded as not relevant to treatment (e.g., the study population was not human; the study population did not include individuals with OCD; the study did not include an intervention intended to treat OCD or OCD symptoms), and 236 articles were retained and reviewed by the authors. Other articles were identified and included during draft development and review.

PSYCHIATRIC MANAGEMENT

ASSESSING THE PATIENT'S SYMPTOMS

Changes in the definition of OCD in DSM-5 (American Psychiatric Association 2013) have no impact on the treatment recommendations of the 2007 guideline. Among the changes are the following in Criterion A: a) *impulse* is changed to *urge* to clarify the difference between OCD and the impulse-control disorders; b) *inappropriate* is changed to *unwanted* to allow for cultural differences in what is regarded as appropriate; c) the wording is changed to reflect that some individuals may not experience marked anxiety or distress in response to their obsessions; d) obsessions are no longer defined as distinct from "excessive worries about real-life problems"; and e) recognition that obsessions are the product of a person's own mind is no longer required. Criterion B, the necessity for insight at some point in the disorder, is deleted. Instead, DSM-5 includes specifiers for clinicians to rate the patient's degree of current insight.

In addition to these changes in the diagnostic criteria for OCD, hoarding disorder is listed as a separate diagnostic category, when this behavior is not the product of OCD obsessions. This change also has no impact on the treatment recommendations of the guideline.

USING RATING SCALES

The 2007 guideline suggests that clinicians encourage their patients to use a self-rated scale to improve self-observation and their recognition of factors that aggravate or ameliorate symptoms. Two new self-report questionnaires for OCD are available in addition to the ones mentioned in the 2007 guideline. The Florida Obsessive-Compulsive Inventory includes a symptom checklist (20 items) and a severity scale (5 items) (Storch et al. 2007b). In a study of 113 patients with OCD, this questionnaire exhibited high internal consistency and high correlation with scores on the clinician-rated Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

An 18-item, validated self-report scale for quantifying levels of distress associated with six OCD symptom subtypes, the Obsessive-Compulsive Inventory–Revised (OCI-R), may be appropriate for both clinical and research purposes (Huppert et al. 2007). The scale devotes three items to each subtype: washing, checking, ordering, obsessing, hoarding, and neutralizing.

Although the original Y-BOCS remains a valid tool, the scale was recently revised to address issues affecting its use (Storch et al. 2010a, 2010b). In the revised version, the Likert rating scale for each item has been expanded from five-point (0–4) to six-point (0–5), the Resistance to Obsessions item was deleted, and the Severity Scale item and scoring were revised to integrate avoidance behaviors. In addition, the Symptom Checklist content and format have been modified to reflect the fact that some OCD symptoms are not fear based.

A scale has also been developed for rating severity of hoarding symptoms. The Saving Inventory–Revised (SI-R) is a reliable, internally consistent scale that can distinguish hoarders from community control subjects and from elderly subjects with a range of hoarding behaviors (Frost et al. 2004). The SI-R produces measures of difficulty discarding, excessive clutter, and excessive acquisition.

An additional easy to use five-item self-report measure is the Hoarding Rating Scale (HRS-SR; Tolin et al. 2008). The HRS-SR is a self-report version of the Hoarding Rat-

ing Scale–Interview and contains five items on difficulty discarding, acquiring, clutter, distress, and impairment rated from 0 (not at all difficult/none) to 8 (extremely difficult/extreme). The self-report version correlated highly with the interview measure (Tolin et al. 2008, 2010).

The guideline notes that "for most patients, OCD seriously impairs quality of life." Newer studies confirm the relationship between symptomatic and functional outcomes. One study examined the relationship of response to disability and health-related quality of life (HRQOL) in patients enrolled in a 24-week placebo-controlled fixed-dose trial (*N*=466) of escitalopram (10 or 20 mg/day), paroxetine (40 mg/day), or placebo, and in patients (*N*=468) enrolled in a separate 40-week flexible-dose (escitalopram 10–20 mg/day), placebo-controlled relapse-prevention trial (Hollander et al. 2010). The relationship of relapse to disability (Sheehan Disability Scale [SDS]) and HRQOL (Medical Outcomes Study Short Form [SF-36]) was investigated using data from this second trial. At both study endpoints, those responding to active drug showed significantly greater improvement on the SDS and the SF-36 compared with those in the placebo group. In the 40-week relapse study, SDS and SF-36 scores were significantly better for those who did not relapse than for those who did.

A German study (*N*=69) evaluated change in HRQOL (using the SF-36) in patients with OCD treated for about 10 weeks in a specialized behavioral program as either inpatients, outpatients, or in a day hospital (with antidepressant or antipsychotic augmentation added as judged clinically necessary) (Moritz et al. 2005). The study confirmed earlier observations of the diminished HRQOL of patients with OCD compared with the general population and of its greater improvement in responders versus nonresponders to treatment.

A 40-week open-label extension trial of controlled-release fluvoxamine in individuals who had completed 12 weeks of double-blind treatment (*N*=56) found that the greater the OCD improvement at 12 weeks, the greater the improvement at week 52 in measures of HRQOL (SF-36) (Koran et al. 2010). HRQOL continued to improve over the 40-week period of open-label treatment.

CHOOSING TREATMENT SETTING

The 2007 guideline recommends that "patients should be cared for in the least restrictive setting that is likely to be safe and to allow for effective treatment." The guideline identifies a number of possible indications for hospital treatment.

Two uncontrolled studies add to the evidence that inpatient treatment can benefit patients with severe OCD who have complicating disorders and have failed to benefit from less intensive interventions. In one study, patients (*N*=52) with severe, chronic, treatment-resistant OCD (Y-BOCS score ≥30; inadequate response to selective serotonin reuptake inhibitor [SSRI] treatment, to augmentation, and to cognitive-behavioral therapy [CBT]) were treated for a mean of 4.5 months in an inpatient setting with CBT in the form of intensive graded exposure and response prevention (ERP) augmented with cognitive restructuring (Boschen et al. 2008). Medications were continued at "the lowest dose compatible with health and symptom reduction." Clinically significant reduction from baseline Y-BOCS scores was seen at 12 weeks (mean decrease 14%) and 24 weeks (mean decrease 31%). In a second inpatient study, 23 adolescents with treatment-resistant OCD, many of whom had comorbid disorders, were observed in a naturalistic study. After 4 to 21 weeks of intensive ERP combined with nursing support and medications (not described), 70% met criteria for clinically significant change. Mean Child Y-BOCS scores fell 40% (Bjorgvinsson et al. 2008).

The 2007 guideline states that home-based treatment may be necessary for patients with hoarding or, initially, for patients with OCD symptoms that are so impairing they cannot come to an office or clinic. A small study (*N*=28) randomly assigned patients to receive fourteen 90-minute sessions of ERP delivered either in an office or at home (or wherever symptoms tended to occur) and found no significant difference in outcome posttreatment or at 3- or 6-month follow-up (Rowa et al. 2007).

ENHANCING TREATMENT ADHERENCE

The guideline highlights the importance of enhancing treatment adherence. The importance of treatment enhancement is supported by findings of a small study (*N*=30), which found, after controlling for baseline symptom severity, that therapist-rated between-session patient adherence to ERP assignments (15 sessions) was a significant predictor of the degree of symptom reduction (Y-BOCS scores) as measured by independent raters (Simpson et al. 2011). Patient adherence during acute ERP treatment also predicted OCD severity at 6-month follow-up (Simpson et al. 2012). In addition, a 10-week, open-label study (*N*=32) of fluvoxamine treatment suggests that encouraging behavioral change may be an important part of pharmacotherapy (Pinto et al. 2007). A questionnaire measure indicating resistance to changing obsessive-compulsive behaviors was associated with achieving less reduction in symptoms.

PROVIDING EDUCATION TO THE PATIENT

The self-help materials and advocacy organizations described in the 2007 guideline remain relevant. Treating clinicians are encouraged to familiarize themselves with

these resources and with newer self-help and patient education materials that include the following:

Abramowitz JS: *Getting Over OCD: A 10-Step Workbook for Taking Back Your Life*. New York, Guilford Press, 2009

Anthony M, Swinson R: *When Perfect Isn't Good Enough: Strategies for Coping With Perfectionism*. Oakland, CA, New Harbinger Publications, 2009

Bell J, Jenike M: *When in Doubt, Make Belief: An OCD-Inspired Approach to Living With Uncertainty*. Novato, CA, New World Library, 2009

DuFrene T, Hyman B: *Coping With OCD: Practical Strategies for Living Well With Obsessive-Compulsive Disorder*. Oakland, CA, New Harbinger Publications, 2008

Rachman S, de Silva P: *Obsessive-Compulsive Disorder (Facts)*, 4th Edition. New York, Oxford University Press, 2009

Steketee G, Frost RO: *Stuff: Compulsive Hoarding and the Meaning of Things*. New York, Houghton Mifflin Harcourt, 2010

Tolin DF, Frost RO, Steketee G: *Buried in Treasures: Help for Compulsive Acquiring, Saving, and Hoarding*. New York, Oxford University Press, 2007

Veale D, Willson R. *Overcoming Obsessive Compulsive Disorder: A Self-Help Guide Using Cognitive Behavioral Techniques*. London, Constable & Robinson, 2009

Yadin E, Foa EB, Lichner TK: *Treating Your OCD With Exposure and Response (Ritual) Prevention: Workbook*. New York, Oxford University Press, 2012

ACUTE PHASE TREATMENT

Studies of OCD treatment commonly define *responders* as individuals who either experience a 25%–35% or greater decrease in Y-BOCS score or have a Clinical Global Impressions–Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved). These definitions are abbreviated in this section as follows: Y-BOCS ≥25%, Y-BOCS ≥35%, and CGI-I:1,2.

CHOOSING AN INITIAL TREATMENT MODALITY

The guideline recommends CBT or a serotonin reuptake inhibitor (SRI; i.e., SSRIs or clomipramine) as first-line treatments for OCD. Choice of treatment modality depends on many factors, including "the nature and severity of the patient's symptoms, the nature of any co-occurring psychiatric and medical conditions and their treatments, the availability of CBT, and the patient's past treatment history, current medications, and preferences."

Guidelines and reviews from other organizations have taken similar positions on these treatments and the supporting evidence. A consensus panel of 30 international experts convened by the World Federation of Societies of Biological Psychiatry (Bandelow et al. 2008) concluded that SSRIs, clomipramine, and CBT either alone or combined with these medications are first-line treatments for OCD. A meta-analysis of OCD treatment studies published between 1980 and 2009 provides an overview of advantages and disadvantages of the treatments usually utilized (Marazziti and Consoli 2010). Guidelines from the British National Institute for Health and Clinical Excellence are available but use cost-benefit criteria that may not have applicability for the U.S. healthcare system (National Institute for Health and Clinical Excellence 2005).

The 2007 guideline recommends that combined treatment should be considered for patients with unsatisfactory response to monotherapy, for those with co-occurring psychiatric conditions for which SRIs are effective, and for those who wish to limit the duration of SRI treatment. A study by Foa et al. (2005) provides additional support for the efficacy of combined treatment for certain patients. In this blinded study, 122 patients with OCD were randomly assigned to receive 12 weeks of ERP, clomipramine, a combination of the two, or pill placebo. Response and remission rates, calculated from the blinded ratings, were higher in both ERP groups than in the clomipramine-alone group and the pill placebo group. Clomipramine alone outperformed placebo. Differing definitions of *response* and *remission* applied to the data post hoc changed the magnitude but not the significance of these differences in outcome (Simpson et al. 2006).

CHOOSING A SPECIFIC PHARMACOLOGICAL TREATMENT

The guideline notes that all SSRIs appear to be equally effective in treating OCD, even though two—citalopram and escitalopram—are not approved by the U.S. Food and Drug Administration (FDA) for this indication. On the basis of available treatment trials, the guideline suggests that greater response and symptom relief may be achieved with an SSRI dose that exceeds the manufacturer's recommended maximum dose. For citalopram, Table 3 of the

guideline describes a "usual target dose" of 40–60 mg/day, a "usual maximum dose" of 80 mg/day, and an "occasionally prescribed maximum dose" of 120 mg/day. Although recent studies provide some additional evidence for the efficacy—and for the tolerability at high doses—of citalopram and escitalopram for OCD, caution is in order. An August 2011 Drug Safety Communication from the FDA states that because of the potential for clinically significant QT_c prolongation, citalopram "should no longer be used in doses greater than 40 mg/day" (FDA Drug Safety Commission 2011). This communication was updated on March 28, 2012, to include steps to be taken if citalopram is used in patients with conditions that increase the risk of QT_c interval prolongation. In addition, for patients older than 60 years of age, the communication states, "the maximum recommended dose is 20 mg/day." In light of this communication, lower doses of citalopram than are described in Table 3 of the guideline are now typically used. Clinicians are encouraged to consult the FDA communication for details.

The studies of high-dose escitalopram include a large, double-blind, placebo-controlled trial, two open-label trials of modest size, and a retrospective case notes review of patients (*N*=26) receiving high doses of various SSRIs, including escitalopram and citalopram (Pampaloni et al. 2010).

In a 24-week double-blind, placebo-controlled study, Stein et al. (2007a) randomly assigned patients to receive escitalopram 10 mg/day (*n*=116) or 20 mg/day (*n*=116), placebo (*n*=115), or an active comparator, paroxetine 40 mg/day (*n*=119). Both doses of escitalopram, along with paroxetine, were superior to placebo at week 12 (Y-BOCS total score mean differences from placebo of –1.97, –3.21, and –2.47). The 20-mg/day escitalopram dose separated from placebo earlier (week 6) than the 10-mg dose (week 16). Primary (Y-BOCS total score) and secondary (Y-BOCS subscores, National Institutes of Health Obsessive-Compulsive Scale, Clinical Global Impressions–Severity, and CGI-I) outcome measures showed continued improvement to week 24.

In a 16-week open-label trial, 27 patients were randomly assigned to receive escitalopram at 20 or 30 mg/day (Dougherty et al. 2009). The 30-mg/day group experienced a significantly greater decrease in Y-BOCS scores (55% vs. 37% decrease), but after differences in baseline measures of anxiety and depression were controlled for, significance was lost. Among study completers, 7 of 11 (64%) who received 30 mg/day were full responders (Y-BOCS ≥25% and CGI-I:1,2) compared with 4 of 11 (36%) of those who received 20 mg/day. The higher dose was well tolerated.

In a second 16-week open-label study, 64 patients who had not achieved "responder" status (Y-BOCS ≥25%) after 4 weeks of escitalopram treatment (1 week at 10 mg/day, 3 weeks at 20 mg/day) were continued on the medication at higher doses (33 patients at doses of 35–50 mg/day) (Rabinowitz et al. 2008). After 12 weeks at higher doses, with no dropouts, 80% of the patients had reached responder status. The higher doses were well tolerated, although one patient became hypomanic at 45 mg/day, with resolution of the hypomania after 10 days at 30 mg/day. Decreased sexual desire affected 21 patients (32%), and erectile difficulties (responsive to tadalafil) were reported by 13 of 34 men (38%). These rates are within the ranges reported for other SSRIs.

The guideline notes the importance, when selecting among the SSRIs, of considering the safety and acceptability of particular side effects for a given patient. Paroxetine was noted to be the SSRI most associated with weight gain. A study examining patients with OCD (*N*=138) 2 years after they had completed a 6-month treatment period with clomipramine or SSRIs (not including escitalopram) found clomipramine associated with the greatest weight increase (2.9±2.6 kg), and fluoxetine (0.5±2.4 kg) and sertraline (1.0±1.7 kg) with the least (Maina et al. 2004). Paroxetine weight gain was intermediate (1.7±2.1 kg). In the clomipramine group, 8 of 23 patients (35%) gained 7% or more body weight, compared with 3 of 21 (14%) in the paroxetine group and less than 10% in the fluoxetine and sertraline groups.

IMPLEMENTING PHARMACOTHERAPY

The guideline notes that most patients will not experience substantial improvement from treatment with an SRI for 4–6 weeks, and some will require 10–12 weeks. Since publication of the guideline, investigators have continued to study how to speed response time to SSRIs. In 2008, a controlled-release formulation of fluvoxamine became available in the United States. In a 12-week large (*N*=253), double-blind, placebo-controlled trial supporting FDA approval, onset of action was earlier (week 2) than had been seen in trials with immediate-release fluvoxamine (Hollander et al. 2003). The new formulation allows a more rapid dose titration than the immediate release formulation, with no loss of tolerability (Hollander et al. 2003).

Possibly accelerating OCD response to SRIs by coadministering other medications has also been investigated. Attempts to utilize gabapentin (Onder et al. 2008) or clonazepam (Crockett et al. 2004) to accelerate SRI response have been unsuccessful. A single-blind, 12-week study (*N*=49) suggested that mirtazapine augmentation

may speed therapeutic response to an SSRI without, however, increasing the likelihood of response. The study compared citalopram 20 mg/day (with the dose titrated to 80 mg/day, as tolerated) plus mirtazapine 15–30 mg/day with the same citalopram doses plus placebo. The citalopram + mirtazapine group experienced a significantly more rapid fall in mean Y-BOCS score for the first 6 weeks and had a greater proportion of "responders" (Y-BOCS ≥35% and CGI-I:1,2) at week 4 (48% vs. 18%) but not at weeks 8 or 12 (Pallanti et al. 2004). Nausea, anxiety, insomnia, and sexual side effects were less common in the citalopram + mirtazapine group, but weight gain was more frequent (50% vs. 25%). The authors noted that the single-blind design and modest mirtazapine doses limit interpretation of the study's results.

MANAGING MEDICATION SIDE EFFECTS

The 2007 guideline discusses in detail the common side effects associated with SSRIs and clomipramine and how to manage them. The guideline also notes side effects reported in clinical trials for other medications, including first- and second-generation antipsychotics, also termed *typical* and *atypical antipsychotics*. New data have identified other potential adverse effects to consider when treating OCD with quetiapine or citalopram.

In 2011, as a result of reports of arrhythmias seen in patients who overdosed on quetiapine, who had certain concomitant medical conditions, or who were concomitantly taking certain other drugs, the FDA required the manufacturer's package insert to include a warning that quetiapine should not be used in patients "taking medications known to cause electrolyte imbalance or increase QT interval" or "in circumstances that may increase the risk of occurrence of torsade de pointes and/or sudden death." The warning details the circumstances in which clinicians should attend to this risk, including when considering combining quetiapine with specified medications. Patients with OCD are not at greater risk of cardiovascular side effects than patients in general. The cardiovascular risks associated with first- and second-generation antipsychotic drugs are reviewed elsewhere (Glassman and Bigger 2001; Titier et al. 2005).

In addition, new information is available on risks of self-harming or suicidal behaviors in patients—particularly children and adolescents—taking antidepressants, including SRIs. As reviewed in the 2007 guideline, in 2004 the FDA issued a black box warning regarding risk of suicide in children and adolescents treated with antidepressants and in 2006 issued a similar warning for young adults ages 18–24 years. The guideline notes that many confounds affect meta-analytical calculations of suicidal behaviors, but nonetheless urges careful monitoring for self-harming or suicidal thoughts or behaviors "particularly in the early phases of treatment and after increases in antidepressant dose." Two recent meta-analyses of the SRIs fluoxetine and venlafaxine did not find that these treatments were associated with an increased risk of suicidal behaviors. In the first meta-analysis, data were pooled from 53 trials of fluoxetine treatment in adults with 16 indications other than major depression (14 psychiatric, including 2 OCD trials with 421 fluoxetine and 144 placebo subjects) (Tauscher0Wisniewski et al. 2007). No significant difference was found between groups randomly assigned to receive either fluoxetine (n=7,066) or placebo (n=4,382) in the risk for FDA codes for completed suicide, preparatory acts, suicidal ideation, and the FDA summary category of "all suicidality." Analysis by age categories, including the category 18–24 years, revealed no significant risk difference for suicidality. In the second meta-analysis, intent-to-treat person-level data were pooled from 21 trials of venlafaxine in depressed adults and 12 adult, 4 geriatric, and 4 youth trials of fluoxetine for depression. The study found no evidence that young adults ages 18–24 receiving active medication experienced an increased suicide risk. In the adult and geriatric patients, those receiving active medication experienced a significant decrease in suicidal thoughts and behavior, but a significant decrease was not seen in youths (Gibbons et al. 2012).

CHOOSING A SPECIFIC FORM OF PSYCHOTHERAPY

Of the available psychosocial treatments, the guideline recommends CBT that relies primarily on behavioral techniques such as ERP as having the strongest evidence base, with a smaller database supporting CBT that utilizes primarily cognitive techniques (i.e., cognitive therapy). The guideline also notes that in studies and in practice, each form of CBT often incorporates elements from the other.

Findings of a meta-analysis using random effects and mixed effects statistical modeling of data from 19 studies published between 1980 and 2006 are consistent with the conclusions from the guideline (Rosa-Alcazar et al. 2008). The meta-analysis found very similar effect size estimates for ERP and cognitive therapy and a somewhat smaller effect size for ERP plus cognitive therapy. Exposure *in vivo* combined with exposure in imagination produced better results than exposure *in vivo* alone. The authors caution, however, that the effect size estimate for cognitive therapy was derived from only three comparisons of treatment versus control groups. They note, moreover, that the greater simplicity of ERP is an important advantage in clinical practice. Thus, they conclude that ERP remains

the treatment of choice and that more research on cognitive therapy for OCD is needed before it can be recommended as a first-line treatment.

More recent studies not included in the meta-analysis continue to support the efficacy of CBT (ERP, cognitive therapy, or their combination) for the treatment of OCD. A randomized, nonblinded study (*N*=57) (Jaurrieta et al. 2008a) comparing outcome after 20 completed sessions of individual (*n*=19) or group CBT (ERP+CT; *n*=19 and 19) versus waitlist control (*n*=19) for patients receiving constant, unspecified psychopharmacological treatment found that both active treatment groups achieved significantly lower Y-BOCS scores than the control group and that the patients receiving individual CBT achieved significantly lower posttreatment Y-BOCS scores than those receiving group CBT. However, those receiving individual CBT had a higher dropout rate (32% vs. 16%). At 6-month and 12-month follow-ups, the 20 patients who completed both treatment and follow-up appeared to have maintained their benefits, with mean scores again lower for the individual CBT subjects (Jaurrieta et al. 2008b). Interpretation is limited by nonblind ratings and by the absence of data on patients who either failed to complete treatment or failed to complete follow-up (18/38=47%).

Findings from a small (*N*=29) open study of cognitive therapy versus a waitlist (Wilhelm et al. 2009) are consistent with those of earlier studies that suggest that cognitive therapy without exposure strategies can be effective for some patients.

Whittal et al. (2010) investigated cognitive therapy for obsessions in OCD subjects who lacked prominent overt compulsions; subjects could have subtle overt compulsions and often had mental compulsions, as indicated by a mean baseline Y-BOCS compulsion score of about 7. This randomized but nonblinded study (N=73) compared 12 sessions of manual-driven cognitive therapy with 12 sessions of manual-driven stress management training (SMT). Unexpectedly, in treatment completers, both treatments were superior to the waitlist control condition in reducing obsessions, although cognitive therapy was statistically significantly more effective than SMT at reducing obsessions and total Y-BOCS scores. At 6- and 12-month follow-ups, however, mean Y-BOCS obsessions and Y-BOCS total scores showed no significant differences between the groups; cognitive outcome measures significantly favored the cognitive therapy group at the 6-month but not at the 12-month follow-up. The effect of SMT in this study was unexpected and requires replication, because two prior studies using SMT in OCD patients did not show a similar effect.

With regard to other psychosocial methods for treating OCD, a randomized, blinded comparison (*N*=79) of eight sessions of acceptance and commitment therapy (ACT) versus eight sessions of relaxation training found a significantly greater decrease in symptoms following ACT, both posttreatment and at 3-month follow-up (mean Y-BOCS score changes from 24.22 to 12.76 and 11.79 vs. changes of from 25.40 to 18.67 and 16.23) (Twohig et al. 2010). ACT involves teaching a willingness to view and accept inner experiences without seeking to change or judge them or letting them define oneself and encouraging the patient to choose to direct his or her behavior toward valued goals. At the follow-up, significantly more ACT patients (46%) than relaxation training patients (18%) were "responders" (Y-BOCS score less than or equal to 14, indicating "mild" severity). A 12-week single-blind Iranian study randomly assigned patients to receive citalopram (20 mg/day; *n*=43) or eye movement desensitization and reprocessing (EMDR; *n*=47; number of sessions unknown) (Nazari et al. 2011). EMDR incorporated elements of cognitive therapy and desensitization in imagination. There were 30 completers in each group (70% and 64%, respectively). Completers' Y-BOCS scores decreased significantly more in the EMDR group. However, the fixed, low dose of citalopram, nonblind ratings, completer analysis, and unstated length, number, and exact cognitive therapy content of the EMDR sessions limit the interpretation of these results.

A 12-month randomized clinical trial exploring the efficacy of treatment with an SSRI alone (*n*=30) compared with an SSRI augmented by supplemental brief dynamic psychotherapy (*n*=27) in patients with OCD and co-occurring major depressive disorder found no greater effect for the combined treatment (Maina et al. 2010).

A review of complementary medicine, self-help, and lifestyle interventions for OCD (Sarris et al. 2012) concluded that controlled studies indicate lack of efficacy for St. John's wort (900 mg/day vs. placebo, *N*=60), the omega-3 fatty acid EPA (2 gm/day vs. placebo, 6 weeks, crossover, *N*=11), and meridian tapping (tapping acupressure; vs. progressive muscle relaxation, nonblind, 4 weeks, *N*=70). Some studies suggested benefit from eight 1-hour sessions of mindfulness meditation (vs. waitlist control, nonblind design, *N*=17) and 3 weeks of electro-acupuncture (nonrandom, nonblind vs. waitlist control, *N*=19), but these studies were methodologically weak.

IMPLEMENTING COGNITIVE-BEHAVIORAL THERAPIES

As noted in the 2007 guideline, CBTs have been effectively delivered in both individual and group sessions. A meta-analysis of 13 studies published between 1991 and 2007 (including four randomized, controlled trials and

four controlled trials) supports the efficacy of group CBT for OCD (Jonsson and Hougaard 2009). The overall pre-post effect size across the 13 studies was large. Treatment ranged from 7 to 16 weekly sessions, each with a mean duration of 2 hours. The dropout rate was 13.5% for group treatment compared with 11.4% for the waitlist control groups.

Group and individual CBT formats seem equally effective. A large (N=110), randomized comparison of 15 weekly sessions of ERP plus cognitive restructuring and psychoeducation found no significant difference in treatment effect size among completers of group versus individual therapy formats. The authors' meta-analysis of combined completer data from their study and three others (Anderson and Rees 2007; Fals-Stewart et al. 1993; Jaurrieta et al. 2008a) also showed no significant difference. However, the dropout rate in one study (Jaurrieta et al. 2008a) was twice as high in the individual compared with the group CBT format.

Methods of enhancing the effectiveness of CBT, in addition to combining CBT with an SRI as recommended in the guideline, continue to be explored. One method is to use motivational interviewing to increase patient engagement with CBT. A Brazilian randomized trial (N=93) reported that adding two 1-hour sessions of motivational interviewing and "thought mapping," as compared with adding 2 hours of education regarding exercise and stopping smoking, enhanced the effect of 12 weekly group CBT (ERP+cognitive therapy) sessions (Meyer et al. 2010). The motivational interviewing group showed significantly greater symptom reduction on blinded Y-BOCS ratings at treatment end and at 3-month follow-up. (Only three patients failed to complete both parts of the study, all in the control group.) Another small study (N=12) randomly assigned patients who had refused ERP to receive four weekly sessions of "readiness intervention" or waitlist and found 86% versus 20% subsequently willing to engage in ERP. However, half of those entering ERP after readiness intervention dropped out. The authors discuss other techniques to reduce dropout (Maltby and Tolin 2005).

On the other hand, a small randomized trial (N=30) found no difference in either patient adherence or patient outcome between those who received 18 sessions over 9 weeks of either standard ERP (n=15) or standard ERP coupled with motivational interviewing strategies (n=15) (Simpson et al. 2010). Both groups experienced clinically significant improvement in OCD symptoms without significant group differences in patient adherence.

Another approach for maximizing ERP efficacy is to use medications to enhance what patients learn during exposures. D-cycloserine (a partial agonist at the *N*-methyl-D-aspartate receptor) facilitates fear extinction in animal models and as a result has been combined with exposure-based treatments to see if it facilitates extinction learning in humans. Three small randomized, placebo-controlled studies have investigated the effects of D-cycloserine augmentation of ERP in OCD. In two studies (N=22 and N=32), D-cycloserine reduced the time to response (Kushner et al. 2007; Wilhelm et al. 2008). A reanalysis of the data from the Wilhelm study confirmed that D-cycloserine does not change overall effectiveness of ERP but speeds up the time to response (Chasson et al. 2010). D-cycloserine appears effective, however, only if administered 2 hours or less before the ERP. A small randomized, double-blind study (N=24) in which D-cycloserine was administered 4 hours before the ERP found no effect on treatment response (Storch et al. 2007a).

In addition to seeking ways to enhance the effectiveness of CBT treatment for OCD, investigators have been seeking ways to make it more cost effective. Potential methods include providing additional sessions only for nonresponders to a brief treatment course (Tolin et al. 2011), utilizing bibliotherapy (Tolin et al. 2007), or delivering CBT sessions via telephone or the Internet. Regarding the latter, computer-guided self-help for OCD, particularly the form known as BTSteps, is under study in the United Kingdom (Kenwright et al. 2005). A randomized trial (N=44) reported that patients who were assigned to 17 weeks of computer-guided BTSteps plus nine scheduled telephone support calls by a psychologist did more ERP homework, had a lower dropout rate, and had greater symptom reduction (via self-ratings) than patients who were assigned to BTSteps plus telephone calls only as requested by the patient. Mean total support call time was 76 minutes for the scheduled patients versus only 16 minutes for those in the patient-requested call group.

A second British study looked at the utility of telephone-based ERP (Lovell et al. 2006). Seventy-two patients were randomly assigned to receive ten 1-hour in-person sessions of ERP or one in-person session followed by eight 30-minute weekly telephone sessions and then a 1-hour in-person final session. Clinical outcome, as reflected in self-rated Y-BOCS scores, was equivalent in the two groups posttreatment, with mean scores in both groups dropping from about 25 to about 14. The study suggests that implementation of ERP by telephone after an in-person visit deserves further investigation in circumstances where in-person treatment sessions are difficult to arrange.

Finally, a Swedish study examined the effects of Internet-based ERP for OCD (Andersson et al. 2012). Called Internet cognitive behavior therapy (ICBT), the intervention consisted of four Internet modules that included psychoeducation, cognitive restructuring, establishing an

individual ERP hierarchy, and a relapse prevention program, followed by six modules focused on daily ERP exercises. Therapists had no face-to-face contact with participants. The attention control condition consisted of online nondirective supportive therapy. After 10 weeks, both treatments led to improvement in OCD symptoms, but ICBT resulted in significantly larger improvements on the Y-BOCS (from 21.4±4.6 to 12.9±6.3 vs. from 20.8±4.0 to 18.9±4.2), with 60% in the ICBT group versus 6% in the control condition showing clinically significant improvement (score decrease ≥2 standard deviations below the mean pretreatment value). The results warrant a replication attempt and suggest that ICBT is efficacious and could substantially increase access to CBT.

PURSUING SEQUENTIAL TREATMENT TRIALS

The guideline provides suggestions and an algorithm (Figure 1; available online at http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1678180) to aid clinicians in choosing sequential treatment trials for patients who do not respond or who partially respond to initial treatments. Options include moving from CBT to an SSRI or vice versa, raising the SRI dose, switching to a different SSRI or clomipramine (with multiple switches possible), and pursuing various augmentation strategies.

As described in the following section, newer studies have strengthened the evidence supporting some of the augmentation strategies described in the guideline—that is, augmentation with ERP, some second-generation antipsychotics, D-amphetamine, topiramate, or ondansetron. In addition, new augmentation strategies have been investigated with positive (memantine, celecoxib, lamotrigine, pregabalin) and negative (glycine, naltrexone) results. In reviewing these new studies, enthusiasm should be tempered by the realization that nonblinded, nonrandomized treatment trials usually report more favorable results than do later, carefully controlled trials. Given the modest evidence base for augmentation with some of the agents described here, their utility in an individual patient should be reevaluated on an ongoing basis.

Serotonin Reuptake Inhibitor Augmentation With Exposure and Response Prevention

The guideline reports that modest evidence supports the augmentation of SRI treatment with ERP in patients with an inadequate or incomplete response to the SRI alone. Three randomized, controlled trials and a naturalistic trial lend increased weight to this observation. One trial (N=108) randomly assigned patients who had obtained some benefit from at least 12 weeks of SRI treatment to receive 17 twice-weekly sessions of ERP (n=54) or stress management training (n=54) (Simpson et al. 2008). Medications were kept stable. The ERP group achieved significantly lower Y-BOCS scores (14.2±6.6 vs. 22.6±6.3), and 74% reached "responder" status (Y-BOCS ≥25%) versus 22% of the group receiving stress management training. In a second randomized, controlled trial, 100 patients who had obtained some benefit from at least 12 weeks of SRI treatment were randomly assigned to receive 8 weeks of the addition of ERP (n=40), risperidone (n=40), or pill placebo (n=20). The ERP group had significantly lower week 8 Y-BOCS scores and higher responder rates (Y-BOCS decrease ≥25%: 80% [ERP], 23% [risperidone], 15% [placebo]) (Simpson et al., in press). In the third trial evaluating added ERP for patients with a partial response to an adequate SRI trial, patients (N=41) were randomly assigned to receive therapist-administered ERP, 15 sessions provided twice weekly (7.5 weeks), or 6 weeks of self-administered, instructional book-guided ERP after some guidance provided face-to-face (Tolin et al. 2007). Intent-to-treat responder rates (CGI-I:1,2), based on nonblind ratings, were 65% and 25%, respectively, and at 6-month follow-up, with patients having been asked not to change medication regimens, these rates were 50% and 25%, respectively. Thus, some patients apparently benefitted from adding self-administered ERP, but therapist-administered ERP was superior. The absence of a placebo CBT group and the non-blind ratings limit the interpretation of these findings. A naturalistic 1-year follow-up study (N=36) reported the results of offering added CBT to OCD patients who had failed at least one adequate SRI trial (Y-BOCS score ≥16) (Tundo et al. 2007). Patients received an average of four CBT sessions per month for 4 months and then one to four sessions per month during some or all of the next 8 months; the range of total CBT hours provided was 6–46, and the mean 30.4 hours. Two patients refused CBT after one session, and 10 dropped out before 12 months. Five of these 10 (50%) reported CBT was ineffective; three more were lost to follow-up. The intent-to-treat analysis indicated that 15 of 36 patients (41%) were CGI-I:1,2 responders.

A randomized study of modest size (N=30) utilizing blinded raters suggests that stepped ERP—three sessions over 6 weeks along with guided bibliotherapy—may help a minority of patients and that some nonresponders can be helped subsequently by 17 twice-weekly standard ERP sessions (Tolin et al. 2011). Only 5 of 18 (28%) patients who began stepped care were initial responders (Y-BOCS score decreased ≥5 points and reaching ≤13) compared with 5 of 12 (42%) who began standard ERP. Ten of the stepped ERP nonresponder group then entered standard ERP, and four became responders. The attrition rate during the study approached 25%, and some responders from

each group relapsed at 3-month follow-up, suggesting that studies to identify both likely responders to stepped ERP and methods of preventing relapse would be valuable. During the trial, a little more than half of each treatment group received stable doses of anti-OCD medications. Unequal amounts of response to ongoing pharmacotherapy may have confounded the results if, for example, many patients in one group had been taking medication at stable doses for 3 months or more (limiting further expected benefit), and many in the other group had been taking medication for only 1 or 2 months (permitting large further benefit from medication).

Serotonin Reuptake Inhibitor Augmentation With an Antipsychotic

Recent studies of augmentation of SRI treatment with a second-generation antipsychotic raise serious doubt about the efficacy of quetiapine, provide more mixed evidence supporting augmentation with risperidone, and suggest that aripiprazole, not described in the 2007 guideline, may be an effective augmentation agent.

With respect to quetiapine augmentation, the 2007 guideline reviews three double-blind, placebo-controlled studies showing mixed evidence for efficacy. Subsequent trials have cast further doubt on quetiapine's effectiveness as an augmentation strategy in treatment-resistant OCD.

A 12-week trial randomly assigned 40 patients whose symptoms were judged to be "unresponsive" after an adequate SRI trial (i.e., failing to reach a Y-BOCS ≥25% criterion) to receive quetiapine, titrated to 400 mg/day in the first 6 weeks (n=20), or placebo (n=20) (Kordon et al. 2008). In the absence of response, quetiapine could be titrated to 600 mg/day in the second 6 weeks. An intent-to-treat, last observation carried forward (LOCF) analysis found no significant difference in endpoint Y-BOCS score decreases (22% vs. 15%) and a statistically insignificant difference in rate of responders (Y-BOCS ≥35%) (quetiapine: 6/18 [33%]; placebo: 3/20 [15%]). The authors note that their trial utilized a higher quetiapine dose than the earlier negative trials and a much larger sample than one of those trials. A possibly confounding factor is that patients who had recently completed at least 20 hours of CBT were allowed to enroll in this trial and to continue the CBT; the authors provide no data regarding the proportion of patients in each treatment group who did so.

A 12-week, double-blind trial indicated little or no therapeutic benefit from quetiapine augmentation (Diniz et al. 2011a). The authors randomly assigned patients (N=54) with CGI-I "minimal improvement" and Y-BOCS score greater than 14 to receive fluoxetine ≤80 mg/day+placebo, fluoxetine ≤40 mg/day+clomipramine ≤75 mg/day, or fluoxetine ≤40 mg/day+quetiapine ≥200 mg/day. The mean final Y-BOCS scores of both the fluoxetine+placebo and the fluoxetine + clomipramine groups (Y-BOCS scores 18 and 18, respectively) were significantly lower than the mean Y-BOCS score of the fluoxetine+quetiapine group (Y-BOCS score = 25), which was virtually unchanged from baseline.

In direct contrast, however, a 10-week, double-blind trial that randomly assigned patients (N=76) who were either drug-free or drug-naïve to receive citalopram 60 mg/day+quetiapine 300–450 mg/day or citalopram + placebo reported significant benefit from added quetiapine (Vulink et al. 2009). In an intent-to-treat LOCF analysis, quetiapine addition was associated with a significantly greater decrease in Y-BOCS score (mean decrease 11.9 ± 7.0 vs. 7.8±6.5) and a significantly greater responder rate (69% vs. 41%; Y-BOCS ≥35% and CGI-I:1,2).

Taken together, the results of these studies suggest that, as an SRI augmentation strategy, adding quetiapine may be effective in only a small subset of patients with treatment-resistant OCD.

With respect to risperidone augmentation, the 2007 guideline reviews studies that provided some modest support of risperidone augmentation in OCD. Subsequent trials have provided a more mixed view of risperidone's effectiveness as an augmentation strategy in treatment-resistant OCD.

Two trials that did not include a placebo control and used single-blind ratings support risperidone's efficacy. In an 8-week single-blind, randomized trial (N=50) of augmentation with either risperidone (1–3 mg/day) or olanzapine (2.5–10 mg/day) in nonresponders (Y-BOCS ≥35% not achieved) to an adequate SRI trial (Maina et al. 2008), no significant difference in responder rates (Y-BOCS ≥35% and CGI-I:1,2; 44% vs. 48%, LOCF) was seen between the two antipsychotics. Amenorrhea was more common in the risperidone group (67% vs. 10%), and weight gain was more common in the olanzapine group (mean 2.80 kg vs. 0.77 kg). The strength of the trial results is limited by the absence of a placebo group and of blinded ratings.

An 8-week single-blind, randomized trial (N=41) with the same design suggests augmentation with risperidone (3 mg/day) or aripiprazole (15 mg/day) is effective in OCD patients who were taking SSRIs (Selvi et al. 2011). Responder (Y-BOCS ≥35%) rates were (nonsignificantly) higher among the risperidone patients (13/18 [72%] for completer analysis, 13 of 20 [65%] for intent-to-treat analysis) than among the aripiprazole patients (6/16 [37.5%] completer, 8/21 [38%] intent-to-treat). These findings are limited by the single-blind ratings, modest sample

size, failure to describe the "adjustment" of drug doses, the 15-mg/day maximum dose for aripiprazole, and the trial's limited duration.

On the other hand, as mentioned earlier, an 8-week randomized, controlled trial (N=100) compared the effects of adding risperidone (n=40), ERP (n=40), and pill placebo (n=20) in 100 adults with OCD who were stable on their SRI for at least 12 weeks at a maximally tolerated dose prior to entry. Responder rates (Y-BOCS ≥25%) were significantly higher for the ERP patients (80%) than for those receiving either risperidone (23%) or placebo (15%). Risperidone was not significantly superior to placebo on any outcome measure (Simpson et al., in press).

Several differences between this study and earlier randomized, placebo-controlled trials supporting risperidone augmentation of SRIs (reviewed in the 2007 guideline) likely explain the different outcomes. First, this study randomly assigned patients who reported at least minimal improvement from their SRI (which is why they were continued on a stable SRI dose, most for far longer than the 12-week minimum). In contrast, the earlier randomized, placebo-controlled studies focused on patients with no more than minimal SRI response. Second, in this new study, only 5% of patients reported a lifetime history of a tic disorder. Importantly, some data suggest that SRI nonresponders (Erzegovesi et al. 2005) or those with tic disorders (Bloch et al. 2006) are most likely to benefit from risperidone augmentation. Finally, the earlier studies randomly assigned patients only to medication and thus probably attracted patients who preferred medication rather than those willing to be randomly assigned to medication or CBT.

Taken together, these study results, like the results for quetiapine, suggest that adding risperidone to SRIs in OCD patients may be effective for only a subset of patients with treatment-resistant illness.

Since the 2007 guideline, some additional support for aripiprazole augmentation has come from a double-blind trial and from small open-label studies. A 16-week double-blind study randomly assigned 38 patients whose symptoms had failed to respond (Y-BOCS ≥16) after 12 weeks of SRI treatment to receive augmentation with aripiprazole (15 mg/day) or placebo (Muscatello et al. 2011). Among aripiprazole subjects, 7 of 18 (39%) were Y-BOCS ≥25% responders and 4 of 18 (22%) were Y-BOCS ≥35% responders. There were no placebo group responders. In a 12-week open-label trial enrolling nine patients with treatment-resistant illness, aripiprazole flexibly dosed from 5 to 20 mg/day (mean 11.2±5.2 mg/day) was associated with a significant improvement in Y-BOCS scores in eight completers (Pessina et al. 2009). Two completers were Y-BOCS ≤35% responders, and one was a Y-BOCS ≥25% responder. Similar results from a similar open-label trial are cited in the guideline (Connor et al. 2005).

As noted in the 2007 guideline, questions remain about the long-term effects and tolerability of antipsychotic augmentation. In a Japanese study investigating longer term outcome of augmentation with second-generation antipsychotics, patients (N=44) who had failed to respond (decrease ≤10% and CGI-I score minimally improved or unchanged) to 12 weeks of an SSRI received augmentation with one of three antipsychotics—olanzapine (1–10 mg/day), quetiapine (25–100 mg/day), or risperidone (1–5 mg/day)—along with ERP (number and length of sessions not described) (Matsunaga et al. 2009). At 1-year follow-up, mean Y-BOCS scores had fallen from 29±9.9 to 19.3±6.8, but this final mean score was considerably higher than that (13.7±4.6) of patients who had responded (Y-BOCS ≥35% and CGI-I:1,2) in the initial 12-week SSRI trial and then received similar ERP (intensity and amount again not described). The authors note that the limited response to augmentation with a second-generation antipsychotic must be weighed against the risk of side effects such as weight gain and metabolic syndrome. Interpretation of the study results is limited by the non-blind ratings, by the very low quetiapine dose (mean 60 mg/day), and by the absence of information regarding the mean SSRI doses attained in the initial 12-week SSRI trial and the amounts of ERP subsequently obtained by the two groups.

Serotonin Reuptake Inhibitor Augmentation With Stimulants

The guideline describes two double-blind, single-dose crossover trials and a number of case reports suggesting an immediate effect of stimulants in reducing OCD symptoms. A 5-week double-blind, randomized study (N=24) of dextroamphetamine (30 mg/day) versus caffeine (300 mg/day) augmentation in patients with treatment-resistant OCD suggests that both stimulants and high-dose caffeine may be effective as augmentation strategies (Koran et al. 2009). Responders (Y-BOCS ≥20%) after 1 week of treatment (D-amphetamine, n=6; caffeine, n=7) entered a 4-week double-blind extension phase. At week 5, mean Y-BOCS score decreases were 48% (range 20%–80%) for the D-amphetamine group and 55% (range 27%–89%) for the caffeine group. Strikingly, 4 of 12 (33%) of the D-amphetamine group and 5 of 12 (42%) of the caffeine group met criteria for full response at the end of week 1 (Y-BOCS ≥35% and CGI-I:1,2), and 33% and 50% met criteria at the end of week 5. The authors contrasted these high response rates with the mean placebo response rate of 11% in double-blind, placebo-controlled augmentation trials of second-generation anti-

psychotics (Khan et al. 2005). The double blind was successfully maintained, and no patient discontinued the trial for side effects, although study drug dose for D-amphetamine was reduced to 15 mg for three patients and for caffeine to 200 mg for three patients because of increased pulse/blood pressure, irritability, or nausea and abdominal pain. The rapid, robust, and sustained response to D-amphetamine and caffeine augmentation argues for additional trials.

Serotonin Reuptake Inhibitor Augmentation With Other Agents

Agents Thought to Modulate Glutamate

Recent evidence suggests that dysregulation involving the excitatory neurotransmitter glutamate may contribute to the pathophysiology of OCD (Pittenger et al. 2011; Wu et al. 2012). Since publication of the open-label study of riluzole reported in the 2007 guideline, there have been additional open-label and small randomized, controlled trials of medications thought to modulate glutamate in patients with treatment-resistant OCD. These data are reviewed here.

On the basis of an open-label trial, the 2007 guideline suggests that topiramate might be an effective augmentation agent. Additional support for this strategy is provided by two double-blind, placebo-controlled trials of modest size. A 12-week trial (N=49) found that a significantly larger proportion of topiramate subjects (n=12; mean dose 180 mg/day) than placebo subjects (n=0) were Y-BOCS ≥25% responders (Mowla et al. 2010). The dropout rates in the two groups were nearly identical: 16.7% and 16.0%. A similar 12-week trial (N=36) that used a higher topiramate dose range found a significant treatment effect on compulsions but not on obsessions or on total Y-BOCS score (Berlin et al. 2011). Topiramate (endpoint dose range 50–400 mg/day; mean dose 179±134 mg/day) was not well tolerated: 5 of 18 subjects (28%) discontinued the drug because of side effects and 7 of 18 (39%) required a dose reduction. These results suggest that if topiramate augmentation is attempted, dose escalation must be cautious.

A 16-week double-blind, randomized, placebo-controlled study (N=40) investigated the effectiveness of augmentation with lamotrigine, titrated over 4 weeks from 25 mg/day to the maximum dose of 100 mg/day, in patients with a Y-BOCS score of 16 or higher after at least 12 weeks of SRI treatment (Bruno et al. 2012). SRI doses were stable for at least 2 months and unchanged during the study. At study end, 10 lamotrigine patients (50%) were Y-BOCS ≥25% responders and an additional 7 (35%) were Y-BOCS ≥35% responders, compared with none of the placebo group. Added lamotrigine was generally well tolerated, although sedation affected four patients (20%). The study's positive results contrast sharply with the negative results of an earlier open-label trial in eight SRI treatment-resistant patients (Kumar and Khanna 2000). Larger controlled trials are warranted.

Small open-label trials and a case-control study suggest that memantine may be an effective augmentation agent, and an Iranian double-blind, placebo-controlled trial reported surprisingly high response and remission rates. In an open-label trial, 14 patients who had failed to respond to a stable SRI dose for at least 12 weeks received memantine augmentation for 12 weeks, starting at 5 mg/day and increasing 5 mg/day each week to 20 mg/day (Aboujaoude et al. 2009). The SRI dose was held constant. At study end, 6 of 14 (43%) were responders (Y-BOCS ≥35% and CGI-I:1,2), all by the end of week 4. No patient withdrew because of side effects. In a second open-label trial, 10 patients with OCD received 12 weeks of memantine at 10 mg twice daily. Y-BOCS scores fell by a mean of 41%, and seven patients experienced a decrease in Y-BOCS score of 45% or more (Feusner et al. 2009). In a case-control study, 22 patients treated in an intensive residential treatment program with standard multimodal treatment received memantine augmentation (mean final dose 18 mg/day) (Stewart et al. 2010). The memantine group experienced a greater mean (±SD) decrease in Y-BOCS score than the matched case control group (7.2±6.4 vs. 4.6±5.9) and was significantly more likely to exhibit a 50% or greater decrease in score (22.7% vs. 4.5%). In the 8-week Iranian trial, OCD patients (N=42) with Y-BOCS scores of 21 or higher were randomly assigned to receive memantine 10 mg/day in week 1 and 20 mg/day thereafter or placebo, added to fluvoxamine 100 mg/day for 4 weeks followed by 200 mg/day. The completer analysis (N=38) found a Y-BOCS ≥35% response rate of 100% in the memantine group versus 32% in the placebo group; 17 of 19 (89%) memantine patients versus 6 of 17 (35%) placebo patients achieved remission (Y-BOCS score ≤16) (Ghaleiha et al. 2013). The findings of these trials strongly suggest benefit, but additional double-blind, placebo-controlled trials of memantine augmentation are needed.

A small (N=10) 8-week open-label study examined augmentation with pregabalin in patients who had not experienced a Y-BOCS ≥35% response after at least 6 months of stable dosing of an SRI plus an antipsychotic (Oulis et al. 2011). Patients received adjunctive pregabalin at 225–675 mg/day (mean maximal dose 405 mg/day). Eight patients (80%) became Y-BOCS ≥35% responders. The authors note that interpretation of these findings is severely limited because half the patients were treated as inpatients and six underwent benzodiazepine withdrawal

during the study's first 4 weeks. Thus, the results may reflect, at least in part, the nonspecific effects of hospitalization and the antianxiety effects of pregabalin substitution for the withdrawn benzodiazepine.

A 12-week double-blind, placebo-controlled Iranian study randomly assigned subjects (*N*=48; 75% women) with inadequate response (Y-BOCS ≥16) to at least 12 weeks of treatment with an SRI to receive *N*-acetylcysteine (up to 2,400 mg/day) or placebo (Afshar et al. 2012). Intent-to-treat analysis indicated a significantly greater decrease in mean Y-BOCS score in the *N*-acetylcysteine group; among study completers (*n*=19 and 20), *N*-acetylcysteine was associated with a significantly higher Y-BOCS ≥35% responder rate (52.6% vs. 15%). Mild to moderate gastrointestinal side effects were more common in the *N*-acetylcysteine group. The authors note that the sulfur smell of the *N*-acetylcysteine tablets may have compromised the blind. Further studies of *N*-acetylcysteine augmentation are warranted.

In a double-blind, randomized trial (*N*=24) of glycine titrated to 60 mg/day, evaluable results were obtained from only 14 patients, including only 5 of 12 (42%) of those receiving glycine (Greenberg et al. 2009). Although the five patients receiving glycine experienced a greater mean decrease in Y-BOCS score (6.04 points vs. 1.00 point), the drug was very poorly tolerated.

Other Agents

A placebo-controlled crossover study of naltrexone augmentation in 10 patients with treatment-resistant OCD failed to observe any benefit (Amiaz et al. 2008).

Two small studies suggest possible effectiveness of ondansetron augmentation in OCD. In the first study, 14 patients with treatment-resistant OCD were maintained on stable doses of SSRIs and antipsychotics while ondansetron was added single-blind, 0.25 mg twice daily for 6 weeks, then 0.5 mg twice daily for 6 weeks. Nine patients (64%) became Y-BOCS ≥25% and CGI-I:1,2 responders, and the mean decrease in Y-BOCS score for the 14 patients was 23.2% (Pallanti et al. 2009). Ondansetron was well tolerated. An 8-week Iranian pilot study with methodological limitations investigated the effectiveness of ondansetron augmentation in patients with OCD whose illness and treatment histories were not assayed. Ratings were apparently not blinded (Soltani et al. 2010). Patients (*N*=42) were randomly assigned to receive fluoxetine 20 mg/day plus ondansetron 4 mg/day or fluoxetine plus placebo. The ondansetron group achieved a significantly lower mean Y-BOCS score and earlier improvement (by week 2). An industry-funded, large-scale, randomized, controlled trial is under way to investigate ondansetron's effectiveness as an augmenting agent in OCD. On December 21, 2012, the manufacturer, Transcept Pharmaceuticals, announced that the primary efficacy endpoint to demonstrate an improvement in OCD symptoms versus placebo was not met (http://ir.transcept.com/releasedetail.cfm?ReleaseID=728327).

In an Iranian study of augmentation with an anti-inflammatory drug, 56 patients were randomly assigned, after a 4-week drug-free period, to receive fluoxetine 20 mg/day plus celecoxib 400 mg/day or fluoxetine 20 mg/day plus placebo (Sayyah et al. 2011). In weeks 2 and 8, the celecoxib group had significantly lower mean Y-BOCS scores. The modest sample size, nonblind ratings, low fluoxetine dose, and absence of patients' treatment histories limit interpretation of the results. Exploratory studies of augmentation with celecoxib could be undertaken, but the possibility of serious cardiovascular and gastrointestinal side effects may limit interest.

Other Somatic Therapies

The guideline recommends that other somatic therapies "should be considered only after first- and second-line treatments and well-supported augmentation strategies have been exhausted." New studies are available on repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and other somatic treatments, but the overall strength of evidence for these treatments remains low.

Controlled trials of rTMS have produced both negative and suggestively positive results; the studies differ in the brain region stimulated and in the nature of the stimulation (high versus low frequency). A 6-week double-blind, randomized trial (*N*=30) found no benefit from adding high-frequency rTMS over the right dorsolateral prefrontal cortex in patients with treatment-resistant OCD who continued their usual pharmacotherapy (Mansur et al. 2011). Several other double-blind, randomized trials of rTMS in this area also found no therapeutic effect (Kang et al. 2009; Prasko et al. 2006; Sachdev et al. 2007; Sarkhel et al. 2010). In contrast, completer analysis of a 4-week double-blind, sham-controlled trial (*N*=21) of low-frequency stimulation in the supplemental motor area reported a higher response rate (Y-BOCS≥25%) with active than with sham treatment (6/9 [67%] vs. 2/9 [22%]) (Mantovani et al. 2010). Another double-blind, sham-controlled trial (*N*=22) of low-frequency stimulation in the supplemental motor area also reported significantly greater reduction in OCD symptoms after 2 weeks of active versus sham treatment (mean Y-BOCS reduction of 15.3 vs. 5.3); those receiving active treatment also had higher response rates (Y-BOCS ≥25%) both at 2 weeks (42% vs. 12%) and at 14-week follow-up (35% vs. 6%) (Gomes et al. 2012).

DBS, for which the 2007 guideline reviews reports involving fewer than 20 patients, continues to be explored. Benefits—as well as serious adverse events—have been observed. Stimulation of the nucleus accumbens in patients with treatment-refractory OCD produced a response rate (Y-BOCS≥35%) of 56% (9/16) in the open 8-month phase of a small study (Denys et al. 2010). "Treatment-refractory" was defined as an insufficient response to adequate 12-week trials of two or more SSRIs, clomipramine, 8 weeks of augmentation with a second-generation antipsychotic, and 16 or more sessions of CBT. In the subsequent double-blind comparison of 2-week periods of sham stimulation (stimulator blindly off) and active stimulation in 14 subjects, the mean Y-BOCS scores were 25% lower during active stimulation. Stimulus-related hypomanic symptoms, not requiring mood stabilizers, were seen in eight patients, mild forgetfulness in five, and word-finding difficulty in three.

A second report describes in detail the evolving methods and results of ventral internal capsule/ventral striatum DBS as used by four collaborating research centers, three in the United States and one in Holland, treating 26 patients with refractory OCD. Long-term follow-up found that the response rate (Y-BOCS ≥35%) increased from 28% at 1 month to 62% (16/26) at last follow-up (24–36 months after surgery) (Greenberg et al. 2010).

A small (N=16) 10-month, double-blind crossover study assessed the safety and efficacy of DBS applied to the subthalamic nucleus (Mallet et al. 2008) in patients with treatment-refractory OCD, defined similarly to the study by Denys et al. (2010). Mean Y-BOCS scores were significantly lower after 3 months of active stimulation than after 3 months of sham stimulation (19±8 vs. 28±7), with a 1-month washout period between these study phases. Serious adverse events included one intracerebral hemorrhage and two infections necessitating removal of the stimulator. Transient hypomania, responsive to adjusting stimulus parameters, was seen in three patients, and depressive symptoms with suicidal ideation during sham stimulation were seen in two patients.

Ablative neurosurgery remains a hazardous, although sometimes effective, intervention for patients with severe and intractable OCD. A long-term follow-up of 25 patients with refractory OCD who had undergone unilateral or bilateral capsulotomy found that 12 (48%) had achieved response (Y-BOCS ≥35%) and 9 (36%) were in remission (Y-BOCS score <16). However, only 3 patients were in remission without adverse effects, and 10 patients had significant problems with executive functioning, apathy, or disinhibition (Rück et al. 2008). A long-term follow-up of 64 consecutive patients with refractory OCD who underwent cingulotomy found that at 5 years, 47% met the criteria for full response (Y-BOCS decrease≥35%), and an additional 22% reached partial response criteria (Y-BOCS decrease ≥25%). Thirty of the patients required at least one additional procedure (either another cingulotomy or conversion to subcaudate tractotomy) (Sheth et al. 2013). As the guideline notes, "DBS and ablative neurosurgical treatment for OCD should be performed only at sites with expertise in both OCD and these treatment approaches."

DISCONTINUATION OF ACTIVE TREATMENT

On the basis of four double-blind discontinuation trials that used different designs and different definitions of relapse, the 2007 guideline states that "rates of relapse appear to be increased after discontinuation of SRI treatment" and recommends that successful medication treatment be continued for 1–2 years before considering a gradual taper.

A 24-week study (N=320) of double-blind discontinuation of escitalopram 10 or 20 mg/day after 16 weeks of open-label treatment supports the advantage of continuing active medication (Fineberg et al. 2007). The relapse rate (an increase of ≥5 points in Y-BOCS score or lack of efficacy judged by the blinded investigator) during the 24-week observation period was significantly higher in the placebo group (52%) than in the group continuing escitalopram (23%). In a meta-analysis, the data from this study were combined with those from the four double-blind discontinuation studies cited in the guideline (Donovan et al. 2010). "Relapse," variously defined in the different studies, occurred in 108 of 474 (22.7%) active drug subjects versus 198 of 476 (41.6%) placebo group subjects over the varying follow-up periods in the studies.

The guideline states that "uncontrolled follow-up studies suggest that CBT consisting of ERP may delay or mitigate relapse when SRI treatment is discontinued." Findings from a 2-year follow-up of patients who had been treated "based on clinical considerations" during a 10-week inpatient stay with CBT alone (n=37) or CBT plus an SRI (n=37) are consistent with this statement. After 10 weeks of treatment, patients in both groups improved significantly, with no group differences. Patients were then followed naturalistically for 2 years posttreatment; whether any patients continued to receive CBT is unclear. Of the 37 patients initially receiving CBT plus an SRI, 17 discontinued their SRI during follow-up. At follow-up, there were no significant differences in OCD

severity between those who did or did not continue their SRI (1-year mean Y-BOCS score 15.6 [8.5] vs. 13.9 [9.5]; 2-year mean score 15.6 [8.7] vs. 13.7 [9.9]) (Kordon et al. 2005). At the same time, the study design (e.g., small sample sizes, lack of randomization, nonblind ratings, inpatient treatment setting, and unknown nature and intensity of the CBT) limits the interpretation of these results.

The guideline states that successful CBT consisting of ERP "should be followed by monthly booster sessions for 3–6 months, or more intensively if response has been only partial." Studies continue to suggest that the acute benefits of CBT (either ERP or cognitive therapy) can be maintained long-term in some patients with OCD. A 2-year follow-up study examined patients who had been randomly assigned to receive group or individual CBT consisting of ERP in one trial and cognitive therapy in the other (Whittal et al. 2008). No significant difference in 2-year outcome was seen between ERP and cognitive therapy in the individual CBT trial, but only a little more than half of each treatment group was available for follow-up evaluation. Although 25 of 41 (61%) patients were taking an SSRI or a tricyclic antidepressant when evaluated, medication status and change in status were unrelated to outcome. A little more than half of each group met "recovery" criteria: Y-BOCS score 10 or lower and a decrease from baseline of 6 or more points. For patients in the group CBT trial, ERP produced a significantly greater Y-BOCS improvement than did cognitive therapy, both posttreatment and at 2-year follow-up, but the mean final difference was small (i.e., 1.3 Y-BOCS points). Among the 45 of 73 (62%) treatment completers available for evaluation after 2 years, a little more than half were taking an SSRI or an antidepressant, and in 18 (40%) recovery criteria were met. The nonblind ratings, intervening treatments, and incomplete follow-up constrain the interpretation of these results, but the favorable long-term outcome of many patients is encouraging.

A 5-year follow-up study of 102 of 122 patients who had participated in one of two randomized, double-blind trials comparing fluvoxamine with cognitive therapy or with ERP indicates that each of these initial treatments is likely to be associated with benefits in the long term (Van Oppen et al. 2005). Because patients received varying treatments in the follow-up period, no conclusions can be reached about the long-term efficacy of the initial treatments. At the follow-up evaluation, 5.5 ± 1.3 years after completing study participation, 19% of patients who had received cognitive therapy and 33% of those who had received ERP were taking an antidepressant, as were 51% of those originally randomly assigned to receive fluvoxamine. The majority (63%) of patients had received additional psychotherapy within the follow-up period. Defining "recovery" as a Y-BOCS score of 12 or lower and 7 or more points below baseline, the authors found statistically insignificant differences in long-term recovery rates among patients receiving the three initial treatments: cognitive therapy 53%, ERP 40%, and fluvoxamine 37%.

PSYCHIATRIC FEATURES INFLUENCING THE TREATMENT PLAN

The 2007 guideline describes psychiatric features that may impact the treatment plan and treatment outcome. New data regarding the impact of hoarding behaviors and of comorbid posttraumatic stress disorder (PTSD), tic disorders, major depressive disorder, and social phobia are reviewed briefly here.

HOARDING BEHAVIORS

The guideline notes that patients with OCD whose predominant or only symptom is pathological hoarding may be less responsive to CBT and to pharmacotherapy than those with other predominant symptoms. Although the guideline reviewed specific treatment programs described in observational studies, carefully controlled trials were lacking. A recent study utilized a waitlist control design in patients with clinically significant hoarding to evaluate the effects of a CBT method that targeted factors thought to underlie hoarding. The method attends to hypothetical deficits in information processing, to problematic beliefs and behaviors, and to avoidance and emotional distress (Steketee et al. 2010). The study randomly assigned 46 hoarders seeking treatment to receive 26 weeks of this CBT method (n=23) or 12 weeks of waitlist (n=23) before beginning the CBT treatment. Two patients refused immediate CBT, two did not complete treatment, and two discontinued the waitlist. At week 12, therapist-rated scores on the SI-R had decreased an average of 15% in the CBT group versus 2% in the waitlist group. Of the 41 hoarders who began CBT, 19 (46%) were rated much improved at the last visit and 10 (24%) were rated very much improved. Although only four patients (10%) dropped out after starting CBT, the difficulties in treating hoarding are illustrated by the fact that the 26 sessions, intended to be weekly, took an average of 49 weeks to complete, and 27 of 73 eligible individuals (37%) declined to participate in the study.

Two open studies with *N*=45 (Gilliam et al. 2011) and *N*=32 (Muroff et al. 2009), both limited by utilizing only self-report measures, found that 16–20 group CBT sessions may be moderately helpful in ameliorating hoarding behavior. The study by Muroff and colleagues included two individual 90-minute in-home sessions; the study by Gilliam and colleagues did not. Whereas the group format may reduce costs of treatment, the authors point out the need to investigate the durability of outcome, outcome predictors, and methods to increase efficacy. Web-based CBT for hoarding is also being investigated. A naturalistic study comparing Web-based self-help (*n*=106) with a waitlist control (*n*=155) reported better self-reported outcome at 6 months in the Web-based self-help group, but the absence of independent observation or random assignment and other methodological weaknesses limit the interpretation of these results (Muroff et al. 2010).

Because individual and group CBT for hoarding is lengthy and costly, a naturalistic study examined the effects of a 13-session support group called the Buried In Treasures (BIT) Workshop, a nonprofessionally facilitated, biblio-based, action-oriented support group using a self-help book on hoarding. The 17 self-identified hoarding participants experienced significant decreases in clutter, difficulty discarding, and excessive acquisition from pre- to posttreatment (Frost et al. 2011). In a follow-up study reported in the same publication, these findings were replicated in 11 subjects, as judged by interview and observational measures performed in the subjects' homes. These same investigators have recently completed a trial in which they randomly assigned patients either to this BIT Workshop (*n*=22) or to a waitlist control (*n*=21). BIT participants who completed the workshop showed significant improvement compared with waitlist participants on all hoarding measures. Moreover, the treatment response rate for the BIT Workshop was similar to that obtained in previous individual and group CBT studies of this patient population (Frost et al. 2012). However, the sample size was relatively small, and participants were highly educated and predominantly female. Replication studies are warranted.

A retrospective analysis of data from a large (*N*=466), 24-week, randomized, double-blind, placebo-controlled study of escitalopram (10 or 20 mg/day) compared with paroxetine (40 mg/day) and placebo was consistent with earlier trials reporting a poorer response of hoarding to pharmacotherapy (Stein et al. 2008). Patients with high scores on a hoarding/symmetry factor derived from the Y-BOCS symptom checklist had a poorer response to treatment with escitalopram and paroxetine at both 12 and 24 weeks. Poorer response was also associated with this factor in a 12-week study of 432 patients with OCD treated in 12 countries with citalopram at 20, 40, or 60 mg/day (Stein et al. 2007b). Neither study reports responder rates or differences in Y-BOCS scores or provides data regarding patients with hoarding as their only symptom.

POSTTRAUMATIC STRESS DISORDER

A recent study of Brazilian outpatients with non-treatment-resistant OCD (*N*=215) retrospectively examined the patients' response to 12 weeks of completing either group CBT or SSRI monotherapy. Those with PTSD (*n*=22) and those with a history of trauma not meeting PTSD criteria (*n*=38) responded as well to the group CBT or to an SSRI as those free of these comorbid conditions (Shavitt et al. 2010).

CHRONIC MOTOR TICS

The guideline describes a few small studies that found that co-occurring chronic motor tics (in the absence of Tourette's disorder) diminished the likelihood of response to fluvoxamine but not to clomipramine. An 8-week open-label trial of fluoxetine in patients both with (*n*=13) and without (*n*=61) chronic motor tics found significant improvement in both groups and similar proportions of patients who had "clinically meaningful improvement" (23% and 26%) (Husted et al. 2007). The authors posit that their results suggest that many patients with OCD with co-occurring chronic motor tics need not be exposed, initially at least, to the risks associated with added antipsychotic drugs. They caution, however, that their study was open label, involved few patients with tics that were not severe, and did not control for comorbid affective or anxiety disorders. A meta-analysis of nine antipsychotic medication augmentation trials in OCD found that the OCD patients with comorbid tics were more likely to benefit than those without tics (Bloch et al. 2006). Comparisons of longer-term response to SSRIs in patients with and without tics are needed.

MAJOR DEPRESSIVE DISORDER

The guideline notes, "In many trials of CBT, but not all, co-occurring major depression has been associated with a poorer OCD outcome." A small, randomized study (*N*=29) in patients with OCD with comorbid major depressive disorder reported higher dropout rates in the two study groups (60% and 58%) and lower recovery rates than are typically seen in CBT trials that exclude patients with comorbid major depression (Rector et al. 2009). The study compared 20 weekly sessions of ERP plus cognitive therapy with 20 such sessions that included CBT (method of Aaron Beck and colleagues) targeting the depression in the first 10 sessions. The high dropout rate severely limits interpretation of the study's results. As the guideline states,

"It may be useful to utilize antidepressant medication, and particularly SRIs, to treat co-occurring major depression before or during a trial of CBT."

A second randomized study supports the need for resolving comorbid mood disorders (Belotto-Silva et al. 2012). The study randomly assigned patients with OCD to receive 12 weeks of either group CBT (ERP plus cognitive therapy; $n=70$) or fluoxetine ($n=88$) at 20–80 mg/day. Comorbid major depressive disorder or dysthymia was associated with a worse response to both treatments, as was comorbid social phobia. Dropout rates were substantial in both groups: 26% and 38%, again emphasizing the guideline's recommendation to attend to factors such as comorbid depression that can influence adherence. The guideline indicates that these influential factors "can be thought of as related to the illness, the patient, the physician, the patient-physician relationship, the treatment, and the social or environmental milieu."

SOCIAL PHOBIA

The 2012 study by Belotto-Silva et al. just described, in which 12 patients with OCD were randomly assigned to receive 12 weeks of either group CBT or fluoxetine, also found that comorbid social phobia was associated with a poorer outcome to both treatments. A second 12-week study comparing patients who dropped out before completing CBT ($n=16$) or SSRI treatment ($n=25$) with an equal number of treatment completers found that social phobia was more common in the noncompleters (Diniz et al. 2011b). Other comorbid conditions associated with dropout were agoraphobia, generalized anxiety disorder, and somatization disorder. Together, these studies suggest that in attempting to treat patients with OCD with co-occurring social phobia, close attention should be paid to treating the social phobia, for example, with an SSRI, clonazepam, or CBT.

CONCLUDING REMARKS

Despite the progress that has been made, research is sorely needed to

- find treatments that are more often and more completely efficacious for patients with OCD,
- identify clinically useful predictors of response to initial and subsequent treatments,
- establish the efficacy and safety of various augmentation strategies over the longer term, and
- identify factors indicating which augmentation strategies should be used at which points for which patients.

Clinicians can help in the discovery of these means to reduce suffering by searching for local, well-designed, and ethically approved studies and encouraging patients to look into such studies and participate. A helpful Web site is clinicaltrials.gov, a federally sponsored, searchable database designed to provide patients, family members, and the public with information about ongoing clinical trials.

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