PRACTICE GUIDELINE FOR THE
Treatment of Patients With Obsessive-Compulsive Disorder

WORK GROUP ON OBSESSIVE-COMPULSIVE DISORDER

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STATEMENT OF INTENT

The APA Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA practice guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document available from the APA Department of Quality Improvement and Psychiatric Services, "APA Guideline Development Process."

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GUIDE TO USING THIS PRACTICE GUIDELINE

The *Practice Guideline for the Treatment of Patients With Obsessive-Compulsive Disorder* consists of three parts (Parts A, B, and C) and many sections, not all of which will be equally useful for all readers. The following guide is designed to help readers find the sections that will be most useful to them.

Part A, "Treatment Recommendations," is published as a supplement to the *American Journal of Psychiatry* and contains general and specific treatment recommendations. Section I summarizes the key recommendations of the guideline and codes each recommendation according to the degree of clinical confidence with which the recommendation is made. Section II is a guide to the formulation and implementation of a treatment plan for the individual patient. Section III, "Specific Clinical Features Influencing the Treatment Plan," discusses a range of clinical considerations that could alter the general recommendations discussed in Section I.

Part B, "Background Information and Review of Available Evidence," and Part C, "Future Research Needs," are not included in the *American Journal of Psychiatry* supplement but are provided with Part A in the complete guideline, which is available in print format from American Psychiatric Publishing, Inc., and online through the American Psychiatric Association (http://www.psych.org). Part B provides an overview of obsessive-compulsive disorder (OCD), including general information on natural history, course, and epidemiology. It also provides a structured review and synthesis of the evidence that underlies the recommendations made in Part A. Part C draws from the previous sections and summarizes areas for which more research data are needed to guide clinical decisions.

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DEVELOPMENT PROCESS

This practice guideline was developed under the auspices of the Steering Committee on Practice Guidelines. The development process is detailed in "APA Guideline Development Process," which is available from the APA Department of Quality Improvement and Psychiatric Services. The key features of this process with regard to this document include the following:

- A comprehensive literature review to identify all relevant randomized clinical trials as well as less rigorously designed clinical trials and case series when evidence from randomized trials was unavailable
- The development of evidence tables that summarized the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes
- Initial drafting of the guideline by a work group that included psychiatrists with clinical and research expertise in obsessive-compulsive disorder
- The production of multiple revised drafts with widespread review (11 organizations and 68 individuals submitted significant comments)
- Approval by the APA Assembly and Board of Trustees
- Planned revisions at regular intervals

Relevant literature was identified through a MEDLINE literature search using PubMed for articles published between 1966 and December 2004, using the keywords ("Obsessive-Compulsive Disorder"[MeSH] OR "Compulsive Behavior"[MeSH]) OR ("obsession"[All Fields] OR "obsessional"[All Fields] OR "obsessions"[All Fields] OR "obsessive"[All Fields]) OR ("compulsion"[All Fields] OR "compulsions"[All Fields] OR "compulsive"[All Fields]). This search yielded 13,182 references, of which 10,756 were in the English language and had abstracts. Additional, less formal literature searches were conducted by APA staff and individual members of the Work Group on Obsessive-Compulsive Disorder. The Cochrane databases were also searched for relevant meta-analyses.

The summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made (indicated by a bracketed Roman numeral). In addition, each reference is followed by a bracketed letter that indicates the nature of the supporting evidence.

Part A

TREATMENT RECOMMENDATIONS

I. EXECUTIVE SUMMARY

A. CODING SYSTEM

Each recommendation is identified as meriting one of three categories of endorsement, based on the level of clinical confidence regarding the recommendation, as indicated by a bracketed Roman numeral following the statement. The three categories are as follows:

[I] Recommended with substantial clinical confidence
[II] Recommended with moderate clinical confidence
[III] May be recommended on the basis of individual circumstances

B. EXECUTIVE SUMMARY

1. Psychiatric Management

Obsessive-compulsive disorder (OCD) seen in clinical practice is usually a chronic illness with a waxing and waning course. Treatment is indicated when OCD symptoms interfere with functioning or cause significant distress [I]. Psychiatric management consists of an array of therapeutic actions that may be offered to all patients with OCD during the course of their illness at an intensity consistent with the individual patient's needs, capacities, and desires [I]. It is important to coordinate the patient's care with physicians treating co-occurring medical conditions, other clinicians, and social agencies such as schools and vocational rehabilitation programs [I]. When OCD is of disabling severity, the psychiatrist may need to write on the patient's behalf to government agencies that control access to disability income, publicly financed health care, or government-supported housing; or to tax authorities, courts, schools, or employers [I]. OCD patients who are parents of young children may want advice regarding the genetic risk of OCD. It is important for clinicians to explain to such patients that the available data indicate an increased but modest risk of OCD in the children of affected individuals; patients wanting more information may be referred to a genetic counselor [I].

a. Establishing a Therapeutic Alliance

Establishing and maintaining a strong therapeutic alliance is important so that treatment may be jointly, and therefore more effectively, planned and implemented [I]. Steps toward this end include tailoring one's communication style to the patient's needs and capacities, explaining symptoms in understandable terms, and being both encouraging and comforting [I]. The excessive doubting that is characteristic of OCD may require special approaches to building the alliance, including allowing the patient extra time to consider treatment decisions and repeating explanations (a limited number of times) [I]. In building the therapeutic alliance, the psychiatrist should also consider how the patient feels and acts toward him or her as well as what the patient wants and expects from treatment [I].

b. Assessing the Patient's Symptoms

In assessing the patient's symptoms with the aim of establishing a diagnosis using DSM-IV-TR criteria, it is important to differentiate the obsessions, compulsions, and rituals of OCD from similar symptoms found in other disorders, including depressive ruminations, the worries of generalized anxiety disorder, the intrusive thoughts and images of posttraumatic stress disorder, and schizophrenic and manic delusions [I].

c. Using Rating Scales

The psychiatrist should consider rating the baseline severity of OCD symptoms and co-occurring conditions and their effects on the patient's functioning, using a scale such as the 10-item Yale-Brown Obsessive Compulsive Scale (Y-BOCS), since this provides a way to measure response to treatment [I]. If a rating scale is not used, it is helpful to document the patient's estimate of the number of hours per day spent obsessing and performing compulsive behaviors, and the degree of effort applied to trying to escape the obsessions and to resisting the behaviors [I]. Recording actively avoided items or situations also provides a useful baseline against which change can be measured [I].

Scales may also be utilized to rate other symptoms, such as depression or degree of disability.

d. Enhancing the Safety of the Patient and Others

The psychiatrist should evaluate the safety of the patient and others [I]. This entails assessing the patient's potential for self-injury or suicide, since individuals with OCD alone or with a lifetime history of any co-occurring disorder have a higher suicide attempt rate than do individuals in the general population. Although acting on aggressive impulses or thoughts has not been reported in OCD, and patients rarely resort to violence when others interfere with their performing their compulsive rituals, it remains important to inquire about past aggressive behavior. OCD patients who fear loss of control may engage in extensive avoidance rituals in an effort to contain their symptoms.

The psychiatrist should understand that individuals with OCD are not immune to co-occurring disorders that may increase the likelihood of suicidal or aggressive behavior. When such co-occurring conditions are present, it is important to arrange treatments that will enhance the safety of the patient and others [I].

Because OCD symptoms can also interfere with parenting, the clinician may have to work with the unaffected parent or social agencies to mitigate the effects of OCD symptoms on the patient's children [II].

e. Completing the Psychiatric Assessment

In completing the psychiatric assessment, the psychiatrist will usually consider all the elements of the traditional medical evaluation [I]. With regard to co-occurring conditions, the psychiatrist should pay particular attention to past or current evidence of depression, given its frequency and association with suicidal ideation and behaviors [I]. Exploration for co-occurring bipolar disorder and family history of bipolar disorder is also important in view of the risk of precipitating hypomania or mania with anti-OCD medications [I]. Other anxiety disorders are common in OCD patients, as are tic disorders, and may complicate treatment planning. Other disorders that may be more common and may complicate treatment planning include impulse-control disorders, anorexia nervosa, bulimia nervosa, alcohol use disorders, and attention-deficit/ hyperactivity disorder. Past histories of panic attacks, mood swings, and substance abuse or dependence are also relevant [I].

It is important to document the patient's course of symptoms and treatment history, including psychiatric hospitalizations and trials of medications (with details on treatment adequacy, dose, duration, response, and side effects) and psychotherapies (with details on the nature, extent, and response to all trials) [I].

The psychiatrist should also assess the patient's developmental, psychosocial, and sociocultural history, including his or her primary support group and sociocultural supports, potential psychosocial stressors, educational and occupational history (including military history), sexual history, and capacity to navigate developmental transitions and achieve stable and gratifying familial and social relationships [I]. In addition, the psychiatrist should evaluate how OCD has interfered with academic and vocational achievement as well as familial, social, and sexual relationships [I]. Having evaluated the symptoms and their effects on well-being, functioning, and quality of life, the psychiatrist should assess the role of the patient's social supports in facilitating treatment and in maintaining or exacerbating symptoms [I].

The psychiatrist should consider whether the OCD is a manifestation of a general medical condition [I]; document current medical conditions, relevant hospitalizations, and any history of head trauma, loss of consciousness, or seizures [I]; and record the presence and severity of somatic or psychological symptoms that could be confused with medication side effects [I]. Current medications and doses, including hormonal therapies, herbal or "natural" remedies, vitamins, and other over-the-counter medications, should be reviewed to assess the potential for pharmacokinetic and pharmacodynamic interactions with psychotropic drugs [I]. Allergies or sensitivities to medications should be recorded [I]. A mental status examination, including an evaluation of insight and judgment, should be performed to systematically collect and record data related to the patient's signs and symptoms of illness during the interview [I].

f. Establishing Goals for Treatment

Clinical recovery and full remission, if they occur, do not occur rapidly. Thus, ongoing goals of treatment include decreasing symptom frequency and severity, improving the patient's functioning, and helping the patient to improve his or her quality of life [I]. Treatment goals also include enhancing the patient's ability to cooperate with care despite the frightening cognitions generated by OCD, minimizing any adverse effects of treatment (e.g., medication side effects), helping the patient develop coping strategies for stressors, and educating the patient and family regarding the disorder and its treatment [I].

g. Establishing the Appropriate Setting for Treatment

The appropriate treatment setting may be the hospital, a residential treatment or partial hospitalization program, home-based treatment, or outpatient care. Treatment should generally be provided in the least restrictive setting that is both safe and effective [I].

h. Enhancing Treatment Adherence

To enhance treatment adherence, the psychiatrist should consider factors related to the illness, the patient, the physician, the patient-physician relationship, the treatment, and the social or environmental milieu [I]. Because the patient's beliefs about the nature of the illness and its treatments will influence adherence, providing patient and family education may enhance adherence [II]. Many patients with OCD benefit from educational materials and access to support groups provided by the Obsessive Compulsive Foundation (www.ocfoundation.org). When a patient has insufficient motivation to participate effectively in treatment, motivational interviewing or other psychosocial interventions designed to enhance readiness for change may be helpful [II]. Because medications used to treat OCD have side effects, particularly at high doses, adherence may be enhanced by informing the patient about any likely side effects, responding quickly to side effect concerns, and scheduling follow-up appointments soon after starting or changing medications [I]. In describing cognitive-behavioral therapy (CBT), it is helpful to advise that it involves confronting feared thoughts and situations, though at a tolerable rate [I]. Practical issues such as treatment cost, insurance coverage, and transportation may need to be addressed. When a patient with OCD refuses or prematurely discontinues treatment, the clinician may wish to recommend that family members and others negatively affected by the OCD seek therapy to help develop strategies to mitigate the effect of the patient's OCD on their lives and to encourage the patient to obtain treatment [II].

2. Choosing an Initial Treatment Modality

In choosing a treatment approach, the clinician should consider the patient's motivation and ability to comply with pharmacotherapy and psychotherapy [I]. CBT and serotonin reuptake inhibitors (SRIs) are recommended as safe and effective first-line treatments for OCD [I]. Whether to utilize CBT, an SRI, or combined treatment will depend on factors that include 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, capacities, and preferences. CBT alone, consisting of exposure and response prevention, is recommended as initial treatment for a patient who is not too depressed, anxious, or severely ill to cooperate with this treatment modality, or who prefers not to take medications and is willing to do the work that CBT requires [II]. An SRI alone is recommended for a patient who is not able to cooperate with CBT, has previously responded well to a given drug, or prefers treatment with an SRI alone [II]. Combined treatment should be considered for patients with an unsatisfactory response to monotherapy [II], for those with co-occurring psychiatric conditions for which SRIs are effective [I], and for those who wish to limit the duration of SRI treatment [II]. In the latter instance, uncontrolled follow-up studies suggest that CBT may delay or mitigate relapse when SRI treatment is discontinued [II]. Combined treatment or treatment with an SRI alone may also be considered in patients with severe OCD, since the medication may diminish symptom severity sufficiently to allow the patient to engage in CBT [II].

Deciding whether to start or stop a psychotropic drug during pregnancy or breast-feeding requires making a risk-benefit calculation with the patient and her significant other; this process may be enhanced by providing clear information, seeking consultation from an obstetrician, and providing counseling over several sessions to help the patient come to terms with the uncertainty of the risks [I].

3. Choosing a Specific Pharmacological Treatment

Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline, which are approved by the U.S. Food and Drug Administration (FDA) for treatment of OCD, are recommended pharmacological agents [I]. Although meta-analyses of placebo-controlled trials suggest greater efficacy for clomipramine than for fluoxetine, fluvoxamine, and sertraline, the results of head-to-head trials comparing clomipramine and selective serotonin reuptake inhibitors (SSRIs) directly do not support this impression. Because the SSRIs have a less troublesome side-effect profile than clomipramine, an SSRI is preferred for a first medication trial [I]. Although all SSRIs (including citalopram and escitalopram) appear to be equally effective, individual patients may respond well to one medication and not to another. In choosing among the SSRIs, the psychiatrist should consider the safety and acceptability of particular side effects for the patient, including any applicable FDA warnings, potential drug interactions, past treatment response, and the presence of co-occurring general medical conditions [I].

4. Choosing a Specific Form of Psychotherapy

CBT that relies primarily on behavioral techniques such as exposure and response prevention (ERP) is recommended because it has the best evidentiary support [I]. Some data support the use of CBT that focuses on cognitive techniques [II]. There are no controlled studies that demonstrate effectiveness of dynamic psychotherapy or psychoanalysis in dealing with the core symptoms of OCD. Psychodynamic psychotherapy may still be useful in helping patients overcome their resistance to accepting

a recommended treatment by illuminating their reasons for wanting to stay as they are (e.g., best adaptation, secondary gains) [III]. It may also be useful in addressing the interpersonal consequences of the OCD symptoms [II]. Motivational interviewing may also help overcome resistance to treatment [III]. Family therapy may reduce inter-family tensions that are exacerbating the patient's symptoms or ameliorate the family's collusion with symptoms [III].

5. Implementing a Treatment Plan

When treatment is initiated, the patient's motivation and adherence may be challenged by factors such as treatment cost and medication side effects. It is essential for the psychiatrist to employ strategies to enhance adherence, as described above in Section I.B.1.h [I].

a. Implementing Pharmacotherapy

For most patients, the starting dose is that recommended by the manufacturer [I]. Patients who are worried about medication side effects can have their medication started at lower doses, since many SSRIs are available in liquid form or in pills that can be split [I]. Most patients will not experience substantial improvement until 4–6 weeks after starting medication, and some who will ultimately respond will experience little improvement for as many as 10–12 weeks. Medication doses may be titrated up weekly in increments recommended by the manufacturer during the first month of treatment [II], or when little or no symptom improvement is seen within 4 weeks of starting medication, the dose may be increased weekly or biweekly to the maximum dose comfortably tolerated and indicated [II]. This maximum dose may exceed the manufacturer's recommended maximum dose in some cases [III]. The treatment trial is then continued at this dosage for at least 6 weeks [II]. Since available trial data suggest that higher SSRI doses produce a somewhat higher response rate and a somewhat greater magnitude of symptom relief, such doses should be considered when treatment response is inadequate [II]. Higher doses may also be appropriate for patients who have had little response to treatment and are tolerating a medication well [I]. If higher doses are prescribed, the patient should be closely monitored for side effects, including the serotonin syndrome [I]. Experience with pharmacotherapy in the elderly indicates that lower starting doses of medication and a more gradual approach to dose increase are often advisable [I]. Medication side effects should be inquired about and actively managed [I]. Useful strategies to manage medication side effects include gradual initial dose titration to minimize gastrointestinal distress [I], addition of a sleep-promoting agent to minimize insomnia [I], modest doses of modafinil to minimize fatigue or sleepiness [III], and use of a low-dose anticholinergic agent to minimize sweating [III]. Sexual side effects may be minimized by reducing the dose [II], waiting for symptoms to remit [II], trying a once-weekly, one-day "drug holiday" before sexual activity [II], switching to another SSRI [II], or adding a pharmacological agent such as bupropion [II].

The frequency of follow-up visits after a new pharmacotherapy is initiated may vary from a few days to two weeks. The indicated frequency will depend on the severity of the patient's symptoms, the complexities introduced by co-occurring conditions, whether suicidal ideation is present, and the likelihood of troubling side effects [I].

b. Implementing Cognitive-Behavioral Therapies

Cognitive-behavioral therapies have been delivered in individual, group, and family therapy sessions, with session length varying from less than 1 hour to 2 hours. One group has explored a computer-based approach coupled with a touch-tone telephone system accessible 24 hours a day. CBT sessions should be scheduled at least once weekly [I]. Five ERP sessions per week may be more effective than once-weekly sessions but are not necessarily more effective than twice-weekly sessions [II]. The number of treatment sessions, their length, and the duration of an adequate trial have not been established, but expert consensus recommends 13–20 weekly sessions for most patients [I]. Clinicians should consider booster sessions for more severely ill patients, for patients who have relapsed in the past, and for patients who show signs of early relapse [II]. When resources for CBT are not available, the psychiatrist can suggest and supervise the use of self-help treatment guides and recommend support groups such as those accessible through the Obsessive Compulsive Foundation [III] (see Appendix).

c. Changing Treatments and Pursuing Sequential Treatment Trials

First treatments rarely produce freedom from all OCD symptoms. When a good response is not achieved after 13–20 weeks of weekly outpatient CBT, 3 weeks of daily CBT, or 8–12 weeks of SRI treatment (including 4–6 weeks at the highest comfortably tolerated dose), the psychiatrist should decide with the patient when, whether, and how to alter the treatment [I]. This decision will depend on the degree of suffering and disability the patient wishes to accept. However, it is important to consider that illness can bring secondary gains and that depressed mood can diminish hopefulness; the psychiatrist may have to address issues such as these when patients are not well motivated to pursue further treatments despite limited improvement [I].

When initial treatment is unsatisfactory, the psychiatrist should first consider the possible contribution of several factors: interference by co-occurring conditions,

inadequate patient adherence to treatment, the presence of psychosocial stressors, the level of family members' accommodation to the obsessive-compulsive symptoms, and an inability to tolerate an adequate trial of psychotherapy or the maximum recommended drug doses [I].

When no interfering factor can be identified, augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment [II]. The psychiatrist should first consider augmentation of SRIs with trials of different antipsychotic medications or with CBT consisting of ERP, or augmentation of CBT with an SRI [II]. Combined SRI and CBT treatment may be provided when the patient has a co-occurring disorder that is SRI-responsive [I] or has a partial response to monotherapy [II]. Combined SRI and CBT treatment may also reduce the chance of relapse when medication is discontinued [II]. Another option in the case of partial response to ERP therapy is to increase the intensity of treatment (e.g., from weekly to daily sessions) [III]. Some evidence suggests that adding cognitive therapy to ERP may enhance the results, but this remains to be established [III].

Patients who do not respond to their first SRI may have their medication switched to a different SRI [I]. A switch to venlafaxine is less likely to produce an adequate response [II]. For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can also be considered [III]. The available evidence does not allow one to predict the chance of response to switching medications. SRI nonresponders, like partial responders, have responded to augmentation with antipsychotic medications [II] or CBT [II].

After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered [III]. These include augmenting SSRIs with clomipramine, buspirone, pindolol, riluzole, or once-weekly oral morphine sulfate [III]. However, morphine sulfate should be avoided in patients with contraindications to opiate administration, and appropriate precautions and documentation should occur. If clomipramine is added, appropriate precautions should be utilized with regard to preventing potential cardiac and central nervous system side effects [I]. Less well-supported monotherapies to consider include D-amphetamine [III], tramadol [III], monoamine oxidase inhibitors (MAOIs) [III], ondansetron [III], transcranial magnetic stimulation (TMS) [III], and deep brain stimulation (DBS) [III]. Intensive residential treatment or partial hospitalization may be helpful for patients with severe treatment-resistant OCD [II]. Ablative neurosurgery for severe and very treatment-refractory OCD is rarely indicated and, along with deep brain stimulation, should be performed only at sites with expertise in both OCD and these treatment approaches [III].

6. Discontinuing Active Treatment

Successful medication treatment should be continued for 1–2 years before considering a gradual taper by decrements of 10%–25% every 1–2 months while observing for symptom return or exacerbation [I]. Successful ERP should be followed by monthly booster sessions for 3–6 months, or more intensively if response has been only partial [II]. In medication discontinuation trials, rates of relapse or trial discontinuation for insufficient clinical response are substantial but vary widely because of major methodological differences across studies. Thus, discontinuation of pharmacotherapy should be carefully considered, and for most patients, continued treatment of some form is recommended [II]. The data suggest that CBT consisting of ERP may have more durable effects than some SRIs after discontinuation, but the observed differences in relapse rates could be explained by other factors.

II. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

The essential features of OCD identified in DSM-IV-TR are "recurrent obsessions or compulsions (Criterion A) that are severe enough to be time consuming (i.e., they take more than 1 hour a day) or cause marked distress or significant impairment (Criterion C)" (1, pp. 456–457). Obsessions are intrusive, persistent, unwanted thoughts, impulses, or images that give rise to marked anxiety or distress. Compulsions are physical or mental acts that the patient feels driven to perform in order to magically prevent some feared event, to undo some thought, or to reduce anxiety or distress.

Compulsive acts—also known as *rituals*—are carried out repetitively, excessively, and usually according to rules or in a rigid manner. Obsessions may occur spontaneously or be evoked by a feared environmental stimulus or event. Mental compulsions such as counting, praying, or reviewing

actions, conversations, or lists are initiated by the patient willfully, with the aim of feeling safer or reducing anxiety or distress.

The most common obsessional themes are fears of being contaminated or spreading contamination, accidentally or purposely harming others, making a significant mistake, committing a religious offense or moral infraction, contracting a disease, and being considered homosexual or committing homosexual or pedophilic acts.

Hoarding, when a symptom of OCD, is not usually feared, though it may be regretted. Individuals with OCD may also obsess about orderliness or symmetry, lucky or unlucky numbers or colors, needing to know or remember, heterosexual acts, or bodily health. Obsessions are often accompanied by a feeling of doubt, uncertainty, or incompleteness that drives repetitive thought or action and are often colored by an inflated estimate of danger, an increased sense of responsibility, or a need for certainty or perfection.

A. PSYCHIATRIC MANAGEMENT

Psychiatric management of OCD is indicated when symptoms interfere with functioning or cause significant distress. Although transient OCD is found in community surveys, OCD seen in clinical practice is usually a chronic illness with a waxing and waning course. With appropriate treatment, OCD symptoms usually improve over weeks or months and may become mild or even subside into remission over months or years. Thus, treatment planning and psychiatric management will be iterative processes adapted to the patient's current status and response to previous interventions.

Psychiatric management encompasses a broad collection of professional actions and interventions designed to benefit the patient. These actions and interventions include providing the following:

- Pharmacotherapy and psychotherapy in the appropriate setting, as indicated by patient preference and clinical judgment;
- Guidance to the patient and involved family members about educational materials that are available in published form and on the Web (see Appendix); and
- Information about local support groups (see Appendix).

Psychiatric management should be offered throughout the course of illness at an intensity consistent with the patient's needs, capacities, and desires. The components of psychiatric management across the stages of illness are described in more detail below.

1. Establish a Therapeutic Alliance

As in all of medicine, the physician first attempts to establish and then to maintain a therapeutic alliance so that the patient's care is a joint endeavor. The therapeutic alliance allows the psychiatrist to obtain the information needed to plan effective treatment. The alliance allows the patient to trust the physician and helps motivate adherence to collaboratively planned treatments. It is important to tailor one's communication style to the patient's needs and capacities, along continua from detailed to general, from biologically to psychosocially framed, and from warm to neutral. Explaining symptoms in understandable terms is both encouraging and comforting to patients. The excessive doubting that is characteristic of OCD may require special approaches to building the alliance. For example, the clinician may need to allow the patient more time to consider treatment decisions and may need to repeat explanations (a limited number of times) and at several visits. Increased attention to excessive worry about medication side effects, perfectionism, or checking behaviors may be needed. Treatment of patients with OCD has a potential for transference and/or countertransference issues that may disrupt adherence and the therapeutic alliance. In building the alliance, the psychiatrist should also consider the patient's feelings and actions toward him or her, as well as why the patient has come to him or her specifically, and why at this point in time. What does the patient want and expect? How are these desires and expectations affected by the patient's cultural background, religious background, beliefs about the illness (its cause, effects, and mechanisms), and experience with past treatments?

2. Assess the Patient's Symptoms

The psychiatrist should assess the patient for symptoms of OCD, guided by the diagnostic criteria of DSM-IV-TR (Table 1).

OCD is likely to be underdiagnosed unless specific screening occurs (2). Screening questions might include some of the following: Do you have unpleasant thoughts you can't get rid of? Do you worry that you might impulsively harm someone? Do you have to count things, or wash your hands, or check things over and over? Do you worry a lot about whether you performed religious rituals correctly or have been immoral? Do you have troubling thoughts about sexual matters? Do you need things arranged symmetrically or in a very exact order? Do you have trouble discarding things, so that your house is quite cluttered? Do these worries and behaviors interfere with your functioning at work, with your family, or in social activities?

As part of the assessment, the psychiatrist must differentiate obsessions, compulsions, and rituals from similar symptoms found in other disorders. Unlike obsessions, de-

TABLE 1. DSM-IV-TR Diagnostic Criteria for 300.3 Obsessive-Compulsive Disorder

A. Either obsessions or compulsions:

Obsessions as defined by (1), (2), (3), and (4):

(1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
(2) the thoughts, impulses, or images are not simply excessive worries about real-life problems
(3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
(4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)

Compulsions as defined by (1) and (2):

(1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
(2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. **Note:** This does not apply to children.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorder; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

With Poor Insight: if, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable.

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pressive ruminations are experienced as consistent with one's self-image or values. They often focus on past events but, like obsessions, may concern possible current or future negative events or anticipated failures. The subject matter of depressive ruminations usually concerns self-criticism, failures, guilt, regret, or pessimism regarding the future. Depressive ruminations do not elicit compulsive rituals. The worries of generalized anxiety disorder focus on real life problems and usually do not lead to compulsive rituals, although, as in OCD, the sufferer may try to convince himself or herself that the fear is groundless or may check on the safety of loved ones. Generalized anxiety disorder may also present as a vague but troubling feeling of foreboding, whereas the obsessions of OCD always have clear content. The intrusive thoughts and images of posttraumatic stress disorder are replays of actual events, not anticipations of future events. Obsessions held with delusional conviction can be distinguished from schizophrenic and manic delusions by the absence of other signs and symptoms of these disorders. Moreover, delusional obsessions will have typical OCD content rather than content related to persecution, grandiosity, passivity experiences, or ideas of reference.

OCD can be differentiated from hypochondriasis by noting that the hypochondriacal fear or belief regarding serious disease arises from misinterpretation of ordinary

bodily signs and symptoms. In OCD such fears arise from external stimuli—for example, a patient fearing he has contracted AIDS because he was served by a waiter wearing a bandage, possibly exposing him to blood. In addition, an individual with hypochondriasis does not have insight into the irrationality of his or her fears and behaviors, whereas some insight is usually present in OCD. In body dysmorphic disorder, the recurrent and intrusive preoccupations are limited to the fear or belief that one has a disturbing physical defect, when in reality the defect is nonexistent or slight. In anorexia nervosa and bulimia nervosa, the intrusive thoughts and irrational behaviors center on weight and its effects on self-evaluation. In contrast to the thoughts and urges of paraphilias, OCD-related sexual obsessions or images (e.g., fears of homosexuality, images of having sex with a child) lead to avoidance behaviors, are morally abhorrent, and are resisted. Similarly, in OCD, obsessions regarding a sexual partner are experienced as alien to the self and are not accompanied by stalking behavior.

Differentiating urges to harm an infant that occur as postpartum symptoms of OCD from superficially similar symptoms of postpartum depression is critical. The OCD urges are not accompanied by depressed mood and are experienced as inconsistent with one's self, are resisted, or induce efforts to neutralize the urges through other behaviors. Although OCD rituals aimed at avoiding harming the infant may interfere with attachment or normal maternal behaviors and may require treatment, there is little risk of direct harm to the infant. In contrast, the impulses or ideas that arise in postpartum depression may be experienced as justified, may not be strongly resisted, and emerge from depressed mood and other signs and symptoms of major depression. In postpartum depression, taking steps to protect the infant may be necessary (3).

Differentiating compulsions from the complex vocal or motor tics sometimes seen in Tourette's disorder can be difficult. Tics, unlike compulsions, are neither preceded by thoughts nor aimed at relieving anxiety or preventing or undoing an external, undesired event (4). DSM-IV-TR (1, p. 108) defines a tic as "a sudden, rapid, recurrent, nonrhythmic, [and] stereotyped motor movement or vocalization." Tics are often preceded by premonitory sensations such as muscular tension and may involve repeating an action until an unpleasant, localized, physical tension or a sense of incompleteness is relieved (5, 6). Complex motor tics can take the form of arranging, ordering, touching, or making objects symmetrical (5). Repeating an action until "it feels right" (e.g., repeatedly closing a door until the right sound or sensation of closure is achieved) may be a complex tic or a compulsion, or reflect elements of both. Complex tics may be more likely in individuals with a personal or family history of motor or phonic tics; individuals with a history of hypersensitivity to sensations associated with scratchy fabrics, the touch of clothing labels, or to uneven shoelaces or socks; and individuals with co-occurring diagnoses of attention-deficit disorder or learning disorder (5).

Differentiating OCD from obsessive-compulsive personality disorder (OCPD) may also be difficult. In addition, OCD and OCPD may co-occur (7, 8). In fact, the greater prevalence of OCPD in first-degree relatives of OCD patients than of control subjects suggests the possibility of a genetic relationship between the two disorders (9). Although hoarding, scrupulosity, perfectionism, and preoccupation with rules, order, and lists may occur in both disorders, a number of factors may help distinguish OCD and OCPD. For example, in OCD, anxiety about feared consequences of forgoing compulsive behaviors is prominent, whereas in OCPD, the focus is on "doing things my way, the right way" (i.e., on the need for control). In OCD, perfectionism and preoccupation with rules is usually focal and limited to feared events; in OCPD these traits globally color the individual's attitudes and behavior. Fundamentally, the person with OCPD experiences the concerns and behaviors as part of the normal self and does not resist them but, to the contrary, considers them valued attributes. Despite the fact that OCPD traits often irritate companions or associates, the individual with OCPD has no desire to change these traits.

3. Consider Rating the Severity of OCD and Co-occurring Symptoms and Their Effects on the Patient's Functioning

Use of the Y-BOCS Symptom Checklist (10), which allows the recording of current and past symptoms, or the 18-item Obsessive-Compulsive Inventory (11) may be helpful. These scales may help document both the variety and the clustering of the patient's symptoms. The Y-BOCS Symptom Checklist lists 40 obsessions, 15 behavioral compulsions, 5 mental compulsions, and 9 miscellaneous compulsions.

The psychiatrist should consider using a rating scale such as the 10-item Y-BOCS scale (10, 12) to record baseline severity since this provides a way to measure response to treatment. The Y-BOCS rating can also be compared with the patient's and the family's impressions of severity. The Y-BOCS scale evaluates obsessions and compulsions separately and, for each of these two symptom dimensions, measures the time spent and the degrees of distress, interference with functioning, resistance to the symptoms, and success in resisting. The Y-BOCS may be found at the following Web sites: http://healthnet.umassmed.edu/mhealth/YBOCRatingScale.pdf or www.peaceofmind.com/YBOCS.pdf. The Obsessive-Compulsive Inventory (11), a self-rated scale, may also be considered. A simpler measure

is a visual analog scale in the form of a thermometer with the bottom labeled "no OCD symptoms" and the top labeled "incapacitating OCD symptoms." Encouraging the patient to use a self-rated scale will help him or her become a better self-observer and may aid in identifying factors that aggravate or ameliorate symptoms. If a rating scale is not used, the psychiatrist should document the patient's estimate of the number of hours per day spent in obsessing and in performing compulsive behaviors, and the degree of effort applied to trying to escape the obsessions (by distraction or accepting passive awareness, not by counterargument) and to resisting the behaviors. Recording items or situations that the patient actively avoids because of OCD also provides a useful baseline against which change can be measured.

The psychiatrist should consider recording co-occurring conditions and their effects on the patient's functioning. For monitoring depression, which is commonly present and may aggravate OCD symptoms, the clinician might also consider self-rated scales. These can be as simple as visual analog scales or scales measuring symptoms of interest using a "0 to 10" severity rating. Formal self-rated scales that may be useful include the Patient Health Questionnaire (PHQ-9) (13, 14), Beck Depression Inventory–II (BDI-II) (15), Zung Depression Scale (16), and the patient versions of the Inventory of Depressive Symptomatology (IDS) or the shorter 16-item Quick-IDS (QIDS) (17).

OCD symptoms may seriously impair self-care, interpersonal relationships, vocational ability, marital and family relationships, child-rearing capacities, and use of leisure time. Thus, it may be useful to include a rating of disability—for example, the self-rated, three-item Sheehan Disability Scale (SDS) (18, 19), which records disability in the domains of work, family, and social relationships. Some patients, however, may not accurately recognize the degree of their disability until after successful treatment. For most patients, OCD seriously impairs quality of life (20). A rating of the patient's quality of life, using a scale such as the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (21) or the more detailed World Health Organization Quality of Life Survey (WHOQOL-100) (22), can provide a broader measure of disease impact and of the results of treatment.

4. Evaluate the Safety of the Patient and Others

In individuals with OCD, as with all psychiatric patients, assessing the risk for suicide and self-injurious behavior, as well as the risk for harm to others, is crucial. Collateral information from family members or others can be helpful in assessing such risks. When these risks are present, it is important to arrange treatments that will enhance the safety of the patient and others. Although accurate prediction of dangerousness to self or others is not possible in a given individual at a given point in time, many factors have been associated with increased risk in groups of individuals and are, therefore, important to determine.

In assessing and estimating the patient's potential for self-injury or suicide, a number of factors should be taken into consideration. Individuals with OCD alone or with a lifetime history of any co-occurring disorder have a higher suicide attempt rate than do individuals in the general population (23, 24). In rare instances, self-injury can also be directly or indirectly associated with compulsive behaviors. Because increased risk of suicide attempts and suicide has been associated with specific psychiatric symptoms and disorders, the psychiatrist will also want to assess for hopelessness, agitation, psychosis, anxiety, or panic attacks, as well as the presence of mood or substance use disorders, schizophrenia, borderline personality disorder, or other disorders associated with heightened risk. Risk for suicide and for suicide attempts is also increased by a history of previous suicide attempts, including aborted attempts. Thus, if a patient has this history, the nature of those attempts and their potential lethality should be determined. It is also essential to determine whether the patient has had thoughts of death, self-harm, or suicide and the degree to which the patient intends to act on any such thoughts. If a patient has considered suicide, the extent of planning or preparation and the relative lethality of any planned suicide methods should be considered. The availability of the means for suicide, including firearms, should also be explored. Also relevant is any family history of suicide, recent exposure to suicide or suicide attempts by others, real or perceived lack of social supports, and recent losses, including impairments resulting from medical conditions. Cultural, religious, and ethnic factors can also modify suicide risk. Further information is available in APA's *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (25).

The psychiatrist should also evaluate the patient's potential for harming others. This evaluation will include inquiring about whether the patient has had thoughts or urges to harm others and when these thoughts and urges have led to aggression toward others in the past. Such questioning should be sensitive to the fact that patients may fear thoughts, impulses, urges, or images related to harming others or to sexually abusing a child, even though these are experienced as alien to the self and true desires. Although acting on such impulses or thoughts has not been reported in OCD, the patient may fear loss of control and engage in extensive avoidance rituals. OCD symptoms can occasionally be associated with direct or indirect potential for

harm to others. For example, OCD symptoms can interfere with parenting, leading the patient, for example, to avoid or neglect his or her children, to "clean" them inappropriately with bleach or other harmful substances, or to insist on inappropriate neatness. In such cases, the psychiatrist may have to work with the unaffected parent or social agencies to mitigate the effects of OCD symptoms on the patient's children. On rare occasions, individuals with OCD have become distressed and aggressive when others interfered with the performance of compulsive rituals. Finally, in assessing the potential for harm to others, the psychiatrist should consider the possibility that aggressive behavior can be associated with co-occurring disorders such as substance use, impulse control, and personality disorders.

5. Complete the Psychiatric Assessment

In completing the psychiatric assessment, the psychiatrist will usually include the elements of the adult general psychiatric evaluation as described in APA's *Practice Guideline for the Psychiatric Evaluation of Adults*, 2nd edition (26). Facets of the assessment that are of particular relevance to individuals with OCD are highlighted in Table 2.

At all phases of subsequent assessment, the psychiatrist should be alert for signs, symptoms, and history suggesting the possibility of co-occurring conditions. Particular attention should be given to mood disorders, since depressive disorders (27, 28) and bipolar disorder (29, 30) are more common in patients with OCD than in the general population. Careful exploration for family history for bipolar disorder is also important in view of the risk of precipitating hypomania or mania with anti-OCD medications.

Other anxiety disorders (panic disorder, generalized anxiety disorder, social phobia) are common in OCD patients (24, 31, 32) and may complicate treatment planning as described later in this guideline (Sections III.A.5 and III.A.6).

Tics are common in individuals with OCD. Conversely, OCD has been diagnosed in 28%–62% of individuals with Tourette's disorder (33). In patients with co-occurring OCD and Tourette's disorder, use of a rating scale such as the Yale Global Tic Severity Scale (YGTSS) (34) may be helpful. This scale provides anchor points for rating the number, frequency, intensity, complexity, interference, and impairment associated with motor and phonic tics.

Anorexia nervosa and bulimia nervosa may be more common in men and women with OCD than in the general population (24, 35). The prevalence of OCD appears to be elevated in patients with either anorexia nervosa or bulimia nervosa (36–38).

Evaluation should also include screening for alcohol or substance abuse or dependence. In some (31, 39) but not all studies (24), an increased risk of alcohol abuse and dependence has been noted. In addition, the presence of a substance use disorder will influence treatment planning (Section III.A.8).

Other disorders with elevated prevalence in OCD include certain impulse-control disorders, such as skin picking and trichotillomania. In children and adolescents with OCD, the prevalence of attention-deficit/hyperactivity disorder (ADHD) and of oppositional defiant disorder (ODD) is elevated (40). Since structured interview instruments lack modules for developmental disorders, the absence of prevalence data regarding ADHD in adult OCD patients may represent an error of omission. Given that about half of early-onset OCD patients with co-occurring ADHD will continue to have clinically significant ADHD symptoms in adulthood, assessing adult OCD patients for ADHD may be helpful. Assessment instruments include the Conners Adult ADHD Rating Scales (CAARS) (41) and the Wender Utah Rating Scale (WURS) (42), among others (e.g., see reference 43).

In assessing the past psychiatric history, a chronological history should be obtained of past psychiatric illnesses, including substance use disorders and treatment, and of hospitalizations. More specifically, the psychiatrist should attempt to document the longitudinal course of the patient's symptoms and their relationship to aggravating or ameliorating factors, including treatment. Details of the patient's past medication trials should be obtained to ensure that drug doses and trial durations have been adequate, to understand side effects and other factors influencing adherence, and to evaluate the degree of response. The nature, extent, and response to all trials of psychotherapy, including cognitive-behavioral therapy, should also be documented. When past medical records are accessible, these can be helpful in augmenting the treatment history provided by the patient. Past histories of psychiatric symptoms or co-occurring disorders will influence treatment planning and should also be elicited, such as alcohol or substance abuse or dependence (Section III.A.8), prominent fluctuations in mood (Section III.A.4), or panic attacks (Section III.A.5).

The general medical history should document any current general medical conditions, recent or relevant hospitalizations, and any history of head trauma, loss of consciousness, or seizures. The psychiatrist should also consider whether the OCD is a rare manifestation of a general medical condition (e.g., brain trauma, stimulant abuse, carbon monoxide poisoning, parkinsonism). Evaluation of such potential etiologies does not require screening with imaging studies (44), as these disorders are usually obvious from history and examination (33). Current medications and doses should be reviewed to determine potential pharmacokinetic and pharmacodynamic inter-

TABLE 2. Highlights of the Psychiatric Evaluation in Obsessive-Compulsive Disorder (OCD)

- Assess the patient's current symptoms
- Consider rating symptom severity
- Evaluate the effects of symptoms on well-being, functioning, and quality of life
- Evaluate the safety of the patient and others
- Be alert to the presence of co-occurring conditions, especially
  - Depressive disorders
  - Bipolar disorder
  - Other anxiety disorders
  - Tics or Tourette's disorder
  - Eating disorders
  - Alcohol or substance abuse or dependence
  - Impulse-control disorders such as skin-picking, trichotillomania
  - Attention-deficit/hyperactivity disorder
- Record the past psychiatric history, especially
  - Course of symptoms
  - Treatment history, including hospitalizations and trials of medications and psychotherapies, with details of treatment adequacy, duration, response, and side effects
  - Past histories of co-occurring disorders that may influence treatment (e.g., mood or substance use disorders; panic attacks)
- Record the general medical history, especially
  - Current general medical conditions
  - Hospitalizations
  - History of head trauma, loss of consciousness, or seizures
  - Current medications, including hormonal therapies, herbal remedies, vitamins, other over-the-counter medications, and other alternative or complementary therapies
  - Allergies or drug sensitivities
- Elicit a review of systems, especially
  - Symptoms that could be confused with medication side effects
- Record the developmental, psychosocial, and sociocultural history, especially
  - Developmental transitions in childhood and adulthood
  - Capacity to achieve stable and gratifying familial and social relationships
  - Sexual history, including baseline dysfunction, nature of relationships, and impulsive or high-risk sexual behaviors
  - Educational and occupational history (including military history)
  - Primary support group and sociocultural supports (e.g., spouse/partner, children, other family and friends, community or faith-based organizations)
  - Potential psychosocial stressors (e.g., housing, finances, transportation, health care access, involvement with social agencies or the justice system)
  - Effects of OCD on schooling, work, and relationships
  - Role of social supports in facilitating treatment or in maintaining or exacerbating symptoms
- Record the family history, especially
  - OCD
  - Other psychiatric disorders (e.g., major depression, bipolar disorder, panic disorder, generalized or social anxiety disorder, substance use disorders)
  - Tics and/or Tourette's disorder

TABLE 2. Highlights of the Psychiatric Evaluation in Obsessive-Compulsive Disorder (OCD) *(continued)*

Perform a mental status examination, especially
Appearance and general behavior, including degree of cooperation
Psychomotor abnormalities (e.g., tics, mannerisms, rituals, abnormal involuntary movements)
Thought process (e.g., circumstantiality)
Thought content (e.g., obsessions, compulsions, phobias, overvalued ideas, ideas of reference, delusions, suicidal or homicidal ideas)
Perceptual disturbances (e.g., illusions, hallucinations)
Sensorium and cognition
Insight (e.g., understanding of the irrationality of OCD symptoms; motivation and expectations for treatment)
Judgment, especially effects of OCD symptoms in day-to-day decision making

actions with psychotropic drugs. Herbal or "natural" remedies must also be inquired about, along with hormonal therapies, vitamins, other over-the-counter medications, and other alternative or complementary treatments. Allergies and sensitivities to medications, including the nature of the patient's reaction, should be recorded. On careful exploration, reactions the patient describes as "allergies" will sometimes turn out to be unpleasant but manageable side effects. In performing the review of systems, the psychiatrist should record the presence and severity of somatic or psychological symptoms that could be confused with medication side effects.

In assessing the patient's developmental, psychosocial, and sociocultural history, the psychiatrist should review the stages of the patient's life, with attention to developmental transitions in childhood and adulthood and the patient's capacity to achieve stable and gratifying familial and social relationships. A sexual history will identify the nature of the patient's sexual relationships, including impulsive or high-risk sexual behaviors. It will also provide baseline information on patient concerns or sexual dysfunctions from which to judge potential side effects of psychotropic medications. An educational and occupational history (including military history) will help in evaluating the extent to which OCD symptoms have interfered with academic or vocational achievement. The psychiatrist should also assess the patient's primary support group and sociocultural supports (e.g., spouse/partner, children, other family or friends, community or faith-based organizations), as well as their possible role in facilitating treatment and in maintaining or exacerbating symptoms. Assessing the family's understanding of the patient's illness and of potential treatments is similarly important for treatment planning. Other specific information that may be relevant to the assessment of psychosocial stressors includes living arrangements; sources of income, insurance, or prescription coverage; access to transportation and health care; and past or current involvement with social agencies or the justice system.

In assessing the family history, the presence of OCD among family members is of interest for how it may affect the patient's expectations about the illness and its treatment. Although OCD is associated with genetic risk, the clinician should not expect concordance of specific OCD symptoms among siblings or across generations, with the possible exception of hoarding and ordering symptoms (45). A family history of other psychiatric disorders (e.g., major depression, bipolar disorder, panic disorder, generalized anxiety disorder, social phobia, substance use disorders) is also relevant, since it contributes to an increased risk of co-occurring disorders that may influence treatment choice. A family history of tics or Tourette's disorder suggests a need for careful exploration of these disorders in the patient, as their presence could influence treatment response.

The mental status examination involves the systematic collection and recording of data related to the patient's signs and symptoms of illness during the interview. The examination includes consideration of the patient's appearance and general behavior, including the patient's degree of cooperativeness. Psychomotor abnormalities (e.g., tics, mannerisms, rituals, abnormal involuntary movements) are also noted. The patient's mood should be assessed, since the presence of mood symptoms may alter cooperation with treatment or suggest a co-occurring mood disorder. In addition to specific obsessions and compulsions, other abnormalities in thought content (e.g., phobias, overvalued ideas, ideas of reference, delusions, suicidal or homicidal ideas) or thought process (e.g., circumstantiality) may be present. Perceptual disturbances (e.g., illusions, hallucinations) or disturbances in sensorium or cognition are less commonly observed and suggest the presence of a co-occurring disorder. Assessing the patient's degree of insight into the irrationality of the OCD symptoms and motivation and expectations of treatment is essential to treatment planning. Also crucial is the degree to which OCD is affecting judgment, as measured by OCD's effects on the patient's management of the ordinary decisions of daily life.

6. Establish Goals for Treatment

Marked clinical improvement, recovery, and full remission, if they occur, do not occur rapidly (46). Thus, persistent goals of treatment include decreasing symptom frequency and severity, improving the patient's functioning, and helping the patient to improve his or her quality of life (in family, social, work/school, home, parental, and leisure domains). Treatment goals also include enhancing the patient's ability to cooperate with care despite the frightening cognitions that are typical of OCD; anticipating stressors likely to exacerbate the condition and helping the patient develop coping strategies; providing assistance and support in dealing with stresses; monitoring the patient's psychiatric status and intervening as indicated; minimizing any adverse effects of treatment (e.g., medication side effects); and educating the patient and family regarding the disorder and its treatment. Reasonable treatment outcome targets include less than 1 hour per day spent obsessing and performing compulsive behaviors; no more than mild OCD-related anxiety; an ability to live with uncertainty; and little or no interference of OCD with the tasks of ordinary living. However, some patients will be unable to reach these targets, despite the psychiatrist's and the patient's best efforts.

7. Establish the Appropriate Setting for Treatment

In general, patients should be cared for in the least restrictive setting that is likely to be safe and to allow for effective treatment. Consequently, the appropriate treatment setting will depend on a number of factors:

a. Hospital treatment (47) may be indicated by suicide risk, an inability to provide adequate self-care, danger to others, need for constant supervision or support, an inability to tolerate outpatient medication trials because of side effects, need for intensive CBT, the presence of medical conditions that necessitate hospital observation while medications are initiated, or by co-occurring conditions that themselves require hospital treatment, such as severe or suicidal depression, schizophrenia, or mania.
b. Residential treatment (48) may be indicated in individuals with severe treatment-resistant OCD, who require multidisciplinary treatment in a highly structured setting that permits intensive individual and group CBT as well as psychopharmacologic management with close monitoring of treatment adherence over a period of several months.
c. Partial hospitalization (49) may be indicated by a need for daily CBT and monitoring of behavior or medications or a supportive milieu with other adjunctive psychosocial interventions, or to stabilize and increase the gains made during a period of full hospitalization. Goals of treatment include restoring the patient's ability to function in daily life without intensive monitoring; reduction of symptoms to a level consistent with outpatient treatment; prevention of relapse; and maintenance and improvement of social functioning.
d. Home-based treatment may be necessary for patients with hoarding or, initially, for those with contamination fears or other symptoms so impairing that they cannot come to the office or clinic. Home-based treatment may also be indicated for individuals who experience symptoms primarily or exclusively at home.
e. Outpatient treatment is usually sufficient for the treatment of OCD, but the intensity may vary from daily psychotherapy, such as intensive CBT, to treatment less than once a week (after achieving substantial symptom reduction and stabilization).

8. Enhance Treatment Adherence

Factors influencing adherence 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 (50). The fears, doubting, and need for certainty that are characteristic of OCD can influence the patient's willingness and ability to cooperate and can challenge the physician's patience. Patients may, for example, obsess about possible medication side effects and, as a result, refuse pharmacotherapy. Cognitive and motivational effects of co-occurring conditions such as major depression must also be taken into account. Thus, it is useful to determine what the treatment will require of the patient and the way in which these requirements match his or her skills, resources, coping methods, priorities, and goals. Providing the patient and family with education (see Appendix) can be beneficial, because the patient's beliefs about the nature of the illness and its treatments will influence adherence. For example, it is important to inform patients about the delay between starting medication and experiencing substantial symptom relief, and the need for extended periods of medication taking (51).

Medication side effects can influence adherence. The patient's culture, however, may limit his or her willingness to report them (e.g., sexual side effects) or how discomfiting they are. Since effective medications differ both in side-effect profiles and in their adverse effects on a given patient, the psychiatrist has many options for responding to the patient's concerns and preferences. Informing the patient about any likely side effects, responding quickly to side effect concerns, and scheduling follow-up appointments soon after starting or changing medications will enhance adherence.

In describing CBT, the clinician should note that it involves confronting feared thoughts and situations, but at a tolerable rate. The therapist is a supportive coach, not a disciplinarian, and encourages behavior change and praises successes while validating the difficulty of confronting the OCD symptoms.

As with all psychotherapies, how the patient thinks, feels, and acts toward the clinician can decrease cooperation with CBT, the only psychotherapy with documented efficacy for OCD. For example, patients may seek excessive reassurance or have difficulty committing to treatment options. These reactions can often be dealt with in the course of CBT. At other times, improving the patient's degree of cooperation may be best accomplished with another form of psychotherapy. Motivational interviewing (52) and other psychosocial interventions designed to enhance readiness for change may help to improve a patient's motivation for treatment. Clinician-related issues in the therapeutic alliance may also interfere with adherence and therapeutic success. Use of consultation can sometimes be helpful in resolving such impediments.

The psychiatrist should also consider the role of the patient's family and social support system in treatment adherence. Family members may be important allies in the treatment efforts (53). By contrast, family members may provide repeated inappropriate reassurance in efforts to reduce the patient's anxiety or inappropriately offer to do the patient's checking rituals so the patient can get more rest. The family or significant others may not understand that OCD is an illness that gives rise to the patient's compulsive behaviors. They may accuse the patient of being weak or "crazy" or may react to symptomatic behavior with inappropriate anger. They may also be adversely affected by rituals, such as excessive cleaning, or by the patient's insistence on avoiding "contaminated" places. Family therapy may be indicated to deal with hostility, dependency, or other family system issues. When a patient with OCD refuses or prematurely discontinues treatment, family members and others negatively affected by the OCD may benefit from therapy. Under these conditions, the goals of therapy may be to reduce the OCD's impact on the rest of the family and to teach family members how to support recovery from OCD.

Finally, practical issues such as treatment cost, insurance coverage, and transportation may need to be addressed. Pharmaceutical companies may provide free medications for patients with severe financial limitations, with the exact criteria differing from company to company. Information on patient assistance programs is available from the pharmaceutical company Web sites, from the Web site of the Partnership for Prescription Assistance (www.helpingpatients.org), and from Rx Assist (www.rxassist.org).

9. Provide Education to the Patient and, When Appropriate, to the Family

Patients often have little knowledge of the nature, biology, course, and treatment of their disorders. Those with childhood onset of OCD may confuse symptoms with aspects of their innate selves. All patients with OCD should be provided with information and access to educational materials explaining the nature of the disorder and the range of available treatments. Education will help destigmatize the illness and allow the patient to make more fully informed decisions about treatments. Education may also increase the patient's motivation and ability to cooperate in care. When appropriate, education should also be offered to involved family members. The appendix to this guideline contains lists of self-help books for patients with OCD and co-occurring OCD spectrum disorders (see also references 33, 54, 55), patient advocacy group Web sites that provide scientifically reliable information, Web sites that provide information on the use of medications in pregnancy and during breastfeeding, and scientifically reliable, broader mental health Web sites. All OCD patients should be made aware of the Obsessive Compulsive Foundation (www.ocfoundation.org), which provides both educational materials and access to support groups.

10. Coordinate the Patient's Care With Other Providers of Care and Social Agencies

The psychiatrist should coordinate the patient's care with physicians treating co-occurring medical conditions, with other clinicians, and with social agencies such as schools and vocational rehabilitation programs. For patients whose OCD symptoms or medications impair dental health, coordination with the patient's dentist will also be useful.

OCD-related functional impairments may involve family, social, academic, or occupational roles or financial problems. Consequently, under some circumstances, the psychiatrist may need to provide government agencies, schools, employers, and others with written documentation on the patient's behalf. For example, the psychiatrist may have to write to the federal Internal Revenue Service and state tax authorities to explain that a patient's hoarding or procrastination has prevented timely filing of income tax returns. A letter regarding special provisions for participation in or excuse from jury duty may also be appropriate. Students may need letters explaining the need for special dormitory living situations or academic accommodations. Employers may need help in understanding what accommodations are appropriate in light of the Americans With Disabilities Act (56), and referral to a state vocational rehabilitation agency or an occupational therapist may be indicated. For OCD of disabling severity, the psychiatrist must be willing to write to government agencies

that control access to disability income, publicly financed health care, or government-supported housing.

OCD patients who are parents of young children may want advice regarding the genetic risk of OCD. The clinician may wish to refer these parents to a genetic counselor, but should be aware of the available data (Section IV.D). The psychiatrist should help patients concerned about the possibility of OCD in their children find clinicians who can conduct an appropriate evaluation. (Educational materials for parents of children with OCD are included in the Appendix.)

B. ACUTE PHASE

1. Choosing an Initial Treatment Modality

CBT and SRIs are recommended on the basis of clinical trial results as safe and effective first-line treatments for OCD. SRIs include clomipramine and all of the SSRIs. Whether to recommend a form of CBT, an SRI, or combined treatment will depend on a number of factors. These include 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. Because most treatment studies have been of 3–4 months' duration, only limited data are available to guide long-term treatment decisions (Section II.C).

The evidence base for the form of CBT that relies primarily on behavioral techniques, such as ERP (57), is the strongest (58–60). Data also support the use of CBT that focuses on cognitive techniques aimed at identifying, challenging, and modifying dysfunctional beliefs (61–64) if these techniques are combined with behavioral experiments. However, some data suggest, and many clinical experts believe, that the most effective form of CBT for OCD integrates exposure, response prevention (behavior that results in not performing rituals), discussion of feared consequences and dysfunctional beliefs, and relapse prevention. There are few data from controlled trials to support cognitive therapy without ERP or behavioral experiments.

CBT alone, consisting of ERP, is recommended as initial treatment for a patient who is not too depressed, anxious, or severely ill to cooperate with this treatment modality, or who prefers not to take medications. The patient must be willing to do the work that CBT requires (e.g., regular behavioral homework).

An SRI alone is recommended for a patient who has previously responded well to a given drug or prefers treatment with an SRI alone. Starting with an SRI alone may enhance cooperation with treatment by diminishing symptom severity. Thus, an SRI alone may also be considered in patients who have severe OCD or are not otherwise able to cooperate with the demands of CBT. An SRI alone may also be necessary if CBT is not accessible or available.

The available data suggest that combining an SRI and CBT consisting of ERP is more effective than monotherapy in some patients but is not necessary for all (65). Combined treatment should be considered for patients with an 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 treatment with medication. In the latter instance, uncontrolled follow-up studies suggest that CBT consisting of ERP may delay or mitigate relapse when SRI treatment is discontinued (66–68). Combined treatment may also be considered in patients with severe OCD, since the medication may diminish symptom severity sufficiently to allow the patient to engage in CBT.

2. Choosing a Specific Pharmacological Treatment

Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline, which are approved by the FDA for treatment of OCD, are recommended pharmacological agents. Although meta-analyses (59, 69, 70) of placebo-controlled trials suggest greater efficacy for clomipramine than for fluoxetine, fluvoxamine, and sertraline, the results of head-to-head trials comparing clomipramine and SSRIs directly do not support this impression (Section V.A.1). Because the SSRIs have a less troublesome side-effect profile than clomipramine (see Section II.B.2.b), an SSRI is preferred for a first medication trial. Although all SSRIs (including citalopram and escitalopram) appear to be equally effective, individual patients may respond well to one and not to another. The reasons for this patient-specific response are unknown, and no demographic or clinical variables are sufficiently accurate predictors of treatment outcome to permit their use in selecting medications (71).

In choosing among the SSRIs, the psychiatrist should consider the safety and acceptability of particular side effects for the patient, including any applicable FDA warnings, potential drug interactions, past treatment response, and the presence of co-occurring general medical conditions. For example, paroxetine, the SSRI most associated with weight gain (72) and the most anticholinergic SSRI, would not be the first choice for patients with obesity, diabetes mellitus, constipation, or urinary hesitancy.

Another factor in choosing among medications is the degree to which they alter metabolism through the hepatic cytochrome P450 enzyme system or uridine 5′-diphosphate glucuronosyltransferases (UGTs), act at the P-glycoprotein

TABLE 3. Dosing of Serotonin Reuptake Inhibitors (SRIs) in Obsessive-Compulsive Disorder (OCD)

SRI	Starting Dose and Incremental Dose (mg/day)[a]	Usual Target Dose (mg/day)	Usual Maximum Dose (mg/day)	Occasionally Prescribed Maximum Dose (mg/day)[b]
Citalopram	20	40–60	80	120
Clomipramine	25	100–250	250	__[c]
Escitalopram	10	20	40	60
Fluoxetine	20	40–60	80	120
Fluvoxamine	50	200	300	450
Paroxetine	20	40–60	60	100
Sertraline[d]	50	200	200	400

[a]Some patients may need to start at half this dose or less to minimize undesired side effects such as nausea or to accommodate anxiety about taking medications.
[b]These doses are sometimes used for rapid metabolizers or for patients with no or mild side effects and inadequate therapeutic response after 8 weeks or more at the usual maximum dose.
[c]Combined plasma levels of clomipramine plus desmethylclomipramine 12 hours after the dose should be kept below 500 ng/mL to minimize risk of seizures and cardiac conduction delay.
[d]Sertraline, alone among the SSRIs, is better absorbed with food.

transporter, or displace drugs tightly bound to plasma proteins (e.g., see references 73–76). Many interactions, however, reflect only in vitro data, and their clinical importance is not established. Citalopram, escitalopram, and sertraline (along with venlafaxine and mirtazapine) have few or no important known drug interactions. Web sites providing data on potential drug interactions include http://medicine.iupui.edu/flockhart and http://mhc.com/Cytochromes. For up-to-date clinical reports of interactions between specific SRIs and other medications, psychiatrists can consult the federal National Library of Medicine database at http://www.ncbi. nlm.nih.gov/entrez/query.fcgi?DB=pubmed, which is also accessible by entering the term "pubmed" in a search engine. Since there are very few serious risks associated with treatment with SSRIs (e.g., the risk of serotonin syndrome from adding an SSRI to an MAOI, tramadol, meperidine, or dextromethorphan [77, 78]), the psychiatrist will much more often have to consider the relative potential for specific SSRIs to interact with the patient's other medications, particularly given the higher doses of SSRIs that are often used in treating OCD.

Although no definitive data are available, the response of first-degree relatives to particular medications may be predictive of the patient's response because of genetic similarity. This is a subject, however, for future research.

a. Implementing Pharmacotherapy

The need to educate the patient about any medication recommended has been emphasized earlier. Table 3 displays suggested starting doses, known effective doses, maximum recommended doses, and maximum doses occasionally prescribed for each SRI. For most patients, the starting dose is that recommended by the manufacturer.

For patients who are worried about side effects, the medication can be started at half the listed dose or less, since many SSRIs (e.g., citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) are available in liquid form or in pills that can be split. Lower initial medication starting doses and more gradual dose titration may also be needed in patients with co-occurring anxiety disorders, who may experience a transient worsening of anxiety symptoms. Experience with pharmacotherapy in the elderly indicates that lower starting doses of medication and a more gradual approach to dose increase are often advisable. Most patients will not experience substantial improvement until 4–6 weeks after starting medication, and some who will ultimately respond will experience little improvement for as many as 10–12 weeks. Available trial data suggest that higher SSRI doses produce a somewhat higher response rate and somewhat greater magnitude of symptom relief (79–82). Some patients, such as those who have had little response to previous treatments and are tolerating the medication well, may benefit from even higher doses than those shown in the last column of Table 3. In these instances, the patient should be closely monitored for side effects, including the serotonin syndrome. Moreover, patients who have not responded to a known effective dose after 10–12 weeks may respond at higher doses (83, 84). For this reason, some clinicians prefer to titrate doses more rapidly (in weekly

increments to the maximum recommended dose if this is comfortably tolerated), rather than waiting for 1–2 months before each dose increment to evaluate results.

No evidence suggests that OCD treatment outcome is related to plasma levels of clomipramine (85), fluoxetine (86), fluvoxamine (87), or sertraline (82). However, these studies were not designed to identify whether rapid or ultrarapid metabolizers of these medications were more likely to be nonresponders.

b. Managing Medication Side Effects

Unlike the SSRIs, clomipramine also blocks norepinephrine reuptake, muscarinic cholinergic receptors, H_1 histamine receptors, and α_1-adrenergic receptors, as well as sodium channels in the heart and brain. Thus, clomipramine is more likely to induce anticholinergic effects such as tachycardia, dry mouth, constipation, and blurred vision, although these typically diminish over time. Clomipramine is also more likely to induce delayed urination or, uncommonly, urinary retention. Histaminic blockade is associated with weight gain and sedation. Adrenergic blockade may lead to orthostatic hypotension and postural dizziness. Sodium channel blockade can induce cardiac arrhythmias or seizures (estimated to occur in 0.7% of patients treated with clomipramine at a dose of up to 300 mg/day for as many as 6 years [88]). In view of clomipramine's less favorable side-effect profile, expert opinion favors one or more SSRI trials before trying clomipramine (89). Starting clomipramine at a dose of 25 mg/day or less will increase its early tolerability (90).

The most common side effects of the SSRIs include gastrointestinal distress (especially in the first weeks of treatment), agitation, insomnia or somnolence, increased tendency to sweat, and sexual side effects, including diminished libido and difficulty with erection and orgasm. A first step in managing any side effect is to consider whether lowering the drug dose may alleviate the side effect without loss of therapeutic effect. When this is not possible, specific interventions may be considered. Gastrointestinal distress can be minimized by starting with low doses; if mild queasiness or nausea occurs, it will usually disappear within 1–2 weeks at a constant dose. Insomnia may respond to the patient's taking the medication in the morning or to standard sleep hygiene measures, or may require addition of a sleep-promoting agent. Fatigue or sleepiness may respond to the addition of modest doses of modafinil (91). Cases of successful treatment of sweating have been reported with low doses of anticholinergic agents such as benztropine (92, 93), and with clonidine (94), cyproheptadine (95), and mirtazapine (96).

Few controlled trials have been published regarding the management of sexual side effects, which may affect one-third or more of patients (97). Management approaches include reducing the dose to the minimal effective dose; waiting for the symptom to remit (which clinical impression suggests may occur within 2 months in about 10% of patients); trying a once-weekly, one-day "drug holiday" before engaging in sexual activity; switching to another SSRI (which may relieve the sexual dysfunction but not control the patient's OCD); or adding a counteracting pharmacologic agent. The drug holiday approach may alleviate difficulties with erection or orgasm but not with libido. It is not effective for fluoxetine because of its long half-life (98) and may induce withdrawal symptoms if attempted with paroxetine or venlafaxine. Taking drug holidays more than once weekly risks a return of OCD symptoms. Case series and primarily uncontrolled studies report modest success in restoring libido, erection, and orgasm by addition of amantadine, bupropion, buspirone, yohimbine, Ginkgo biloba extract (99), ropinirole (100), or stimulants such as methylphenidate or dextroamphetamine. Adding bupropion has the best evidence base (101), but even this literature is mixed (102). Case series and uncontrolled studies report modest success in restoring erection or orgasm, but not libido, with cyproheptadine or mirtazapine (99). Controlled trials support the use of sildenafil, tadalafil, and vardenafil (103, 104) to restore erection and, in men (105) and women (106), to restore orgasmic ability.

Primarily on the basis of data in children and adolescents (Section III.B.4), concerns have been raised about the potential for increases in self-harming or suicidal behaviors in individuals treated with antidepressant medications, including SRIs. A meta-analysis in adults treated with SSRIs did not demonstrate increases in rates of suicide or suicidal thoughts, although there was weak evidence for an increase in self-harming behavior (107). A second meta-analysis noted an increase in the odds ratio for suicide attempts but did not report on the risk of other suicidal behaviors (108). However, interpretation of these results is difficult because of the confounds involved in calculating risks of suicide and other suicidal behaviors from meta-analyses (109). This is particularly true with regard to the use of antidepressants to treat OCD, because the majority of SSRI clinical trials involve depressed subjects, not subjects with OCD. In addition, studies using other methodologies, including a nested case–control study (110), a retrospective analysis of a large sample of computerized health plan records (111), and a large prospective effectiveness study in adult subjects with bipolar disorder (112), showed no increases in the likelihood of suicide or suicide attempts with antidepressant treatment. An additional nested case–control study also showed no increase in the risk of suicide but did note a small increase in the likelihood of self-harm (113). Although antidepressant

treatment in adults does not appear to be associated with an increase in suicide, it is conceivable that side effects (e.g., anxiety, agitation, insomnia, irritability) may increase the chance of self-harming behaviors in some individuals (109). Thus, careful monitoring for such side effects, as well as for evidence of self-harming or suicidal thoughts or behaviors, is important, particularly in the early phases of treatment and after increases in antidepressant dose. Against these small risks, the benefits of antidepressant treatment must always be considered (114, 115).

SSRIs may be associated with increased intra-operative blood loss in patients also taking nonsteroidal anti-inflammatory drugs (116) and, along with clomipramine, may interact with anesthetics and opiate pain relievers. Patients should inform their surgeon and anesthesiologist if they are taking an SRI.

A drug discontinuation syndrome consisting most often of dizziness, nausea/vomiting, headache, and lethargy, but also including agitation, insomnia, myoclonic jerks, and paresthesias (117, 118), may occur if medication is suddenly stopped. The syndrome may occur after stopping any SRI but is most often seen after rapid discontinuation of paroxetine or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine (117). Particularly for these latter medications, a slow taper over several weeks or more will minimize the likelihood of discontinuation symptoms. If symptoms do occur, raising the medication dose and slowing the taper may bring relief.

3. Choosing a Specific Form of Psychotherapy

CBT is the only form of psychotherapy for OCD whose effectiveness is supported by controlled trials. There are no controlled studies that demonstrate effectiveness of dynamic psychotherapy or psychoanalysis in dealing with the core symptoms of OCD. Psychodynamic psychotherapy may still be useful in helping patients overcome their resistance to accepting a recommended treatment by illuminating their reasons for wanting to stay as they are (e.g., best adaptation, secondary gains). It may also be useful in addressing the interpersonal consequences of the OCD symptoms (119). Motivational interviewing may also help overcome resistance to treatment. As noted in Section II.B.1, the CBT variant that relies primarily on behavioral techniques such as ERP has the strongest evidence base (59, 60). Some data suggest that ERP is more effective if it integrates habituation with discussions of feared consequences and dysfunctional beliefs (120, 121) and with relapse prevention (122–125). For OCD patients without co-occurring depression, data from one large (N=122) randomized controlled trial suggest that intensive CBT consisting of ERP may be superior to clomipramine monotherapy (123, 126).

Data also support CBT that primarily utilizes cognitive techniques such as identifying, challenging, and modifying dysfunctional beliefs when these techniques are combined with behavioral experiments (64, 121, 127–129), which can resemble ERP depending on how they are done. In direct comparisons, CBT utilizing cognitive techniques and behavioral experiments had efficacy similar to CBT consisting of ERP that focused only on habituation. Whether incorporating cognitive techniques with ERP is more effective than either treatment alone is under investigation (122). Only case reports support attempting to treat OCD with cognitive therapy alone, without exposure or behavioral experiments (129, 130). No controlled trials have evaluated other psychosocial methods for treating OCD that have been used in clinical practice (e.g., the "brain-lock technique" [131], other mindfulness approaches, acceptance and commitment therapy).

4. Implementing Cognitive-Behavioral Therapies

Cognitive-behavioral therapies have been delivered in individual, group (132–134), and family therapy sessions, with session length varying from less than 1 hour to 2 hours (135, 136) (for a summary of group and family therapy studies, see references 136, 137). One group has explored the delivery of behavior therapy by means of a self-instructional workbook that allows the patient to design and implement an individualized treatment plan. The patient couples the plan with a voice-activated telephone-response system accessible 24 hours a day to monitor and report progress (138, 139). The literature and expert opinion suggest that CBT sessions should be scheduled at least once weekly (63, 140). One study suggests that five sessions per week of CBT consisting of ERP may be more effective than once-weekly ERP sessions, but are not necessarily more effective than twice-weekly ERP sessions (141). The number of treatment sessions, their length, and the duration of an adequate trial have not been established, but expert consensus recommends 13–20 weekly sessions for most patients (140). More severely ill patients may require longer treatment and/or more frequent sessions. On the basis of clinical experience, clinicians should also consider booster sessions for more severely ill patients, patients who have relapsed in the past, and patients who show signs of early relapse. Finally, because the majority of treatment trials have been only 8–16 weeks long, the long-term persistence of treatment effects and the utility of periodic "booster sessions" require further study.

The psychiatrist may elect to conduct CBT or to refer the patient for this or another adjunctive psychotherapy. Psychiatrists wishing to utilize various forms of CBT are encouraged to pursue training through workshops, conferences, and other training programs. In addition, they can consult a number of treatment manuals (128, 142–

146) or other publications (33, 147–149) or obtain consultation from a clinician specializing in the use of CBT. The psychiatrist initiating CBT should explain to the patient the nature of the treatment, including its here-and-now focus, the rationale underlying treatment procedures, and what the patient will be required to do. When resources for CBT are not available, the psychiatrist can suggest and supervise the use of self-help treatment guides (Appendix) and recommend support groups such as those accessible through the Obsessive Compulsive Foundation (Appendix), although these interventions have not been subjected to controlled study.

At the start of therapy, the psychiatrist can use the Y-BOCS Symptom Checklist (10) to help the patient create a list of target symptoms, including obsessions, compulsions, and items or situations that are avoided because of OCD concerns. The patient ranks the listed items from least to most anxiety-provoking.

In CBT consisting of ERP, patients are taught to confront feared situations and objects (i.e., exposure) and to refrain from performing rituals (i.e., response prevention). Exposures may include in vivo confrontations (e.g., touching objects in public bathrooms) and imaginal confrontations of feared consequences (e.g., imagining becoming "dirty" from "contamination"). Exposures that provoke moderate anxiety are prescribed first, followed as quickly as tolerable by exposures of increasing difficulty. Moving at too slow a pace can diminish faith in the treatment and motivation to continue. Patients must face their fears for a prolonged period without ritualizing, allowing the anxiety or discomfort to dissipate on its own ("habituation"). The goal is to weaken the connections between feared stimuli and distress and between carrying out rituals and relief from distress.

As noted earlier, ERP can be combined with formal cognitive techniques aimed at dysfunctional beliefs (122). Dysfunctional beliefs in OCD include magical thinking (e.g., contamination by proximity), an inflated sense of responsibility for unwanted events, overestimations of the probability of feared events, the assumption that thoughts are morally equivalent to actions or inevitably lead to action ("thought-action fusion"), perfectionism, the belief that anxiety/ discomfort will persist forever, and the need for control. Whether ERP with cognitive therapy is superior to ERP alone is currently under investigation. However, many experts believe that integrating exposures (or behavioral experiments) with discussions of dysfunctional beliefs and feared consequences is likely to be the most effective treatment (120). Modifications of ERP that include formal cognitive techniques as well as other interventions have been suggested for OCD patients with certain symptoms (e.g., hoarding [150]) and those without overt rituals (e.g., see references 59, 149, 151).

5. Monitoring the Patient's Psychiatric Status

The frequency of follow-up visits after a new pharmacotherapy is initiated may vary from a few days to 2 weeks. The indicated frequency of visits will depend on the severity of the patient's symptoms, the complexities introduced by co-occurring conditions, whether suicidal ideation is present, and the likelihood of troubling side effects. Patients should be seen as often as necessary for psychiatric management. They should be encouraged to telephone between visits if medication questions arise. If telephone calls become reassurance rituals, the physician should work with the patient and the patient's family to limit call frequency, using exposure (e.g., to the anxiety that prompts the urge to call) and response prevention (e.g., limiting calls), just as in treating any other ritual.

As noted earlier, symptom rating scales can sometimes be helpful for monitoring the response of OCD, co-occurring depression, or co-occurring anxiety disorders, or for keeping an objective record over time in those patients whose symptoms do not respond to initial treatments. Although use of scales is not expected in routine practice, keeping an objective record over time for patients who do not respond to initial treatments may be helpful.

6. Determining When and Whether to Change Treatments

The physician's goals are always to reduce suffering and disability while minimizing the adverse effects of treatment. First treatments rarely produce freedom from all OCD symptoms. In clinical trials, OCD "responders" are variously defined as those whose Y-BOCS scores decrease by at least 25%–35% from baseline or who are rated much improved or very much improved on the Clinical Global Impressions–Improvement scale (CGI-I) (152). But even these degrees of improvement leave much room for additional gains. Thus, the psychiatrist must decide with the patient when, whether, and how to alter the treatment approach.

Deciding whether to alter the treatment approach will depend on the degree of suffering and disability the patient wishes to accept. Because illness can bring secondary gains (familial attention and caring and freedom from responsibilities), and because depressed mood can diminish hopefulness, the psychiatrist may have to address these issues when the patient is not well motivated to pursue further treatments despite limited improvement in his or her OCD. In the opinion of CBT experts, 13–20 sessions of weekly outpatient CBT with daily homework or weekday daily CBT for 3 weeks (about 50 hours, half therapist-guided, half homework) is an adequate dose after which next steps can be considered (140). With regard to SRIs, expert opinion supports changing medication strategy (switching or augmenting) after a trial of 8–12 weeks, with at least 4–6 weeks at the highest comfortably tolerated

TABLE 4. Factors to Consider at Each Treatment Step

Patient's motivation and ability to comply
Nature and severity of OCD symptoms
Co-occurring psychiatric disorders and their treatment
Presence/absence of suicide risk
Co-occurring medical disorders and their treatment
Likely drug side effects
If patient is a woman of childbearing age or is elderly
Patient's past treatment history
Stressors
Family or caregivers' involvement in symptoms
Cultural issues
Patient's preferences regarding treatment modality, acceptable risks, and expected benefits

dose (140). However, some patients may respond simply to a longer period of continued treatment with the same medication (84). There is no apparent relationship between OCD treatment outcome and plasma levels of SRIs (82, 85–87).

When the outcome of initial treatment has been unsatisfactory, the psychiatrist should first consider the possible contribution of several factors: problems in the therapeutic alliance; interference by co-occurring conditions such as panic disorder, major depression, alcohol or substance use disorders, or severe personality disorder; inadequate patient adherence to treatment; the presence of psychosocial stressors; the level of family members' accommodation to the obsessive-compulsive symptoms (153); and an inability to tolerate an adequate trial of psychotherapy or the maximum recommended drug doses. The psychiatrist should next consider extending or intensifying the psychotherapeutic or pharmacotherapeutic intervention. Figure 1 displays a treatment algorithm outlining potential next steps; Table 4 lists factors to be considered at each treatment step.

7. Pursuing Sequential Treatment Trials

When the patient has an inadequate response to the initial treatment and no interfering factor can be identified, the psychiatrist and patient must decide on next treatment steps without the benefit of data from controlled trials comparing all the possibilities. The sequence of treatment trials shown in Figure 1 is based on expert opinion (e.g., reference 140 and contributors to this guideline).

Given the absence of definitive trial data, augmentation strategies might be preferred to switching strategies in patients who have had a partial response to the initial treatment. Modest evidence supports augmentation of SRIs with antipsychotic medications, including haloperidol (154), risperidone (155–157), quetiapine (158), or olanzapine (159). These trials report response rates in the range of 40% to 55%. Patients who do not respond to one antipsychotic augmenting agent may respond to another. A chart review study found that discontinuing successful augmentation after 1–12 months resulted in relapse for more than 80% (15/18) of patients, most within 2 months of discontinuation (160). Despite these promising data regarding antipsychotic augmentation in OCD, many questions about this treatment strategy remain unanswered, including the optimal dose for each drug, long-term tolerability, when and how to discontinue treatment, the drugs' relative augmentation efficacy, and the reasons that only some patients benefit. Further data are also needed on subsets of patients who may respond preferentially to specific augmentation strategies. For example, one study (154) suggests that augmentation with haloperidol helps only those patients with co-occurring tic disorders.

Modest evidence supports augmentation of SRIs with CBT (specifically, ERP) (161–163) and augmentation of CBT with SRIs (164, 165). Some studies have demonstrated no added benefit from combining SRIs and CBT (61, 123), but these findings are limited by high refusal and dropout rates and uncertainty about levels of treatment resistance (166, 167). Some evidence suggests that adding cognitive therapy to ERP may enhance the results, but this remains to be established. In the absence of definitive data, combination treatment is provided in clinical situations that include efforts to treat a co-occurring disorder that is SRI responsive, to augment a partial response to monotherapy (163), and to reduce the chance of relapse when medication is discontinued (67).

For patients who do not respond to their first SRI, expert opinion and clinical trial data support switching to a different SRI (85, 87, 168–171). However, the evidence does not allow one to predict the patient's chance of response to the new SRI. Clinical experience suggests that response rates to a second SRI trial are close to 50% but may diminish as the number of failed adequate trials increases. A switch to venlafaxine at doses ranging from 225 mg/day to 350 mg/day is supported by active comparator trials and open-label studies suggesting its effectiveness in treating OCD (171–173). A switch to mirtazapine is supported by one open pilot study and a double-blind discontinuation trial (174).

If the strategies described above are not effective, augmentation with other pharmacotherapies may also be considered. Expert opinion (140, 175) and three open-label studies (176–178) support clomipramine augmentation of SSRIs. If clomipramine is added, plasma levels of clomipramine and desmethylclomipramine should be assayed 2–3 weeks after reaching a dose of 50 mg/day, and the total

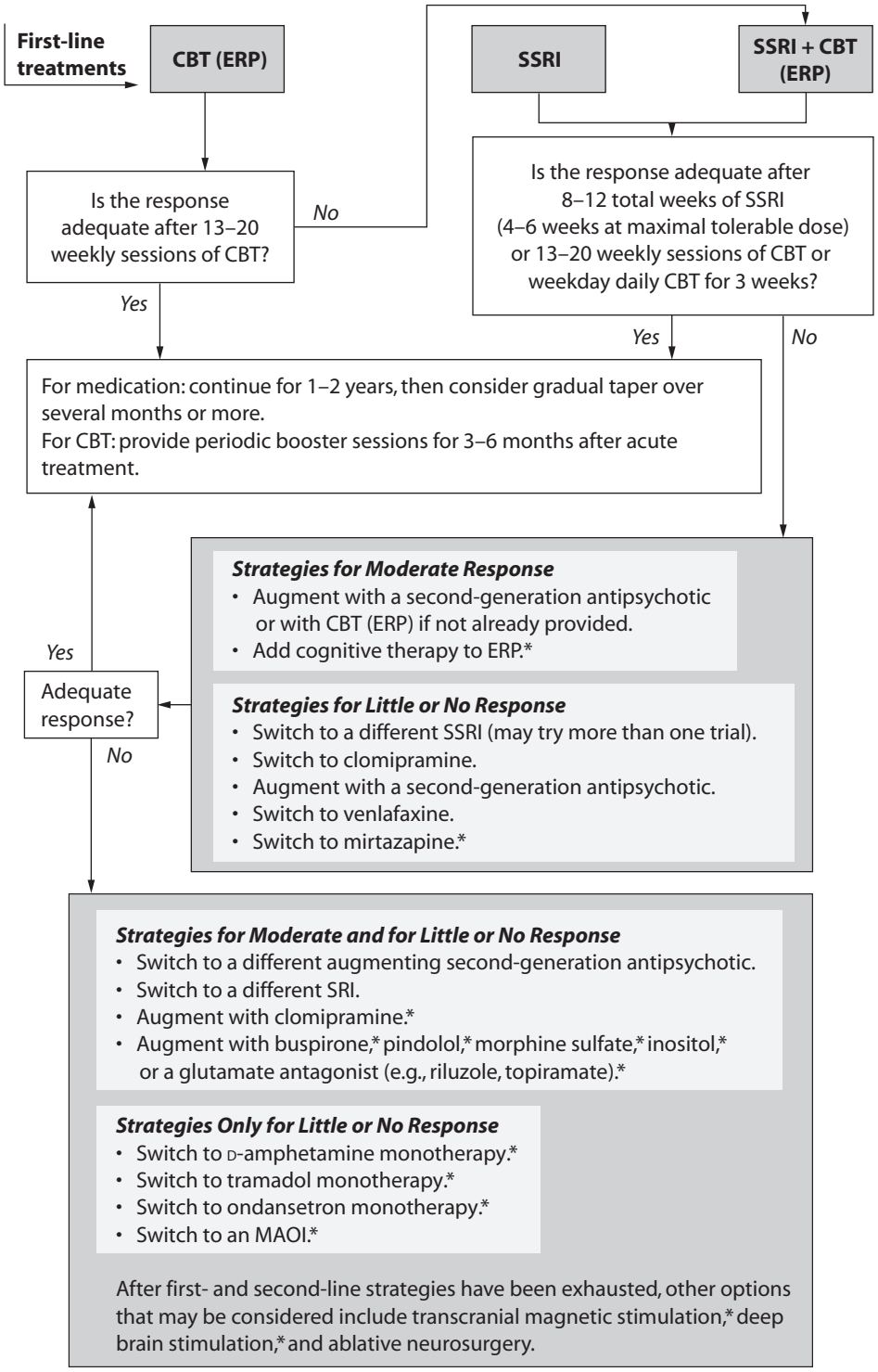

FIGURE 1. Algorithm for the Treatment of Obsessive-Compulsive Disorder (OCD)

Note. "Moderate response" means clinically significant but inadequate response.

*Treatment with little supporting evidence (e.g., one or few small trials or case reports or uncontrolled case series).

CBT = cognitive-behavioral therapy; ERP = exposure and response prevention; MAOI = monoamine oxidase inhibitor; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

plasma concentration should be kept below 500 ng/mL to avoid cardiac and central nervous system toxicity. Fluvoxamine most increases plasma clomipramine levels (178), but substantial increases may occur with fluoxetine and paroxetine. A screening electrocardiogram may be advisable in patients suspected of having heart disease or in patients over the age of 40. Pulse rate and blood pressure should be monitored as the dose of clomipramine is increased.

Positive case reports exist for lithium augmentation, and positive case series have been reported for buspirone augmentation. However, small controlled but methodologically limited trials of lithium and buspirone augmentation have been negative. Adding pindolol 2.5 mg three times daily was effective in one small, double-blind, placebo-controlled trial (179) but not in another (180). A small, 12-week, open-label study reported that augmentation of SRIs with riluzole 50 mg two times daily was often helpful, but methodological limitations prevent confidence that the benefit was due to riluzole itself (501). Small controlled augmentation trials with L-triiodothyronine and desipramine have produced generally negative results, and a double-blind, placebo-controlled trial found St. John's wort to be no better than placebo (181).

Adding once-weekly oral morphine sulfate 30–45 mg to various SSRIs with or without other augmenting agents was superior to placebo in a double-blind crossover study (182). However, morphine sulfate should be avoided in patients with contraindications to opiate administration, including a history of substance or prescription medication abuse, psychosis, mania, antisocial personality disorder, chronic obstructive pulmonary disease, or cardiovascular compromise. In addition, the psychiatrist should consider what precautions and documentation may be needed—for example, those described by the American Academy of Pain Medicine (www.painmed.org). In addition, positive case reports exist, along with a positive case series, for monotherapy with the weak narcotic agonist tramadol (183). And two small, double-blind, placebo-controlled, single-dose studies reported positive results for D-amphetamine 30 mg in unmedicated OCD subjects (184, 185). However, these drugs should be avoided in some patients (e.g., those with a history of alcohol or other substance abuse or dependence).

Other treatment strategies that are supported only by case series, case reports, or small open trials—literatures that are less likely to include negative experiences—include anticonvulsants, MAOIs, ondansetron, L-tryptophan, nicotine delivered via transdermal patch or chewing gum (186), and Kundalini yoga. For patients with severe treatment-resistant OCD, partial hospitalization (49, 187) and intensive residential treatment (48, 188,189) have been used.

Other somatic therapies should be considered only after first- and second-line treatments and well-supported augmentation strategies have been exhausted. With treatments such as these for which efficacy is uncertain, it is especially important to weigh the potential benefits against the side effects and other risks of therapy. For example, evidence for the use of electroconvulsive therapy (ECT) in OCD is limited to a single case series using a nonstandard form of ECT administration (190). In addition, ECT carries the risks of anesthesia and has side effects such as memory impairment. As a result, ECT cannot be recommended for the treatment of OCD but may be considered for treating co-occurring conditions for which it may be indicated (e.g., major depression, uncontrollable mania, and schizophrenia) (191–194). Transcranial magnetic stimulation (TMS) is associated with less potential for side effects, but evidence for its efficacy is limited. Deep brain stimulation (DBS), a reversible and adjustable neurosurgical intervention, has been reported to show efficacy in a few case series of individuals with severe, highly treatment-resistant OCD (195) but also has potential side effects.

The efficacy of ablative neurosurgery (anterior capsulotomy, limbic leucotomy, cingulotomy, and gamma-knife radiosurgery) in patients with severe, treatment-refractory, or intractable OCD has been evaluated in case reports and unblinded studies. Improvement rates have ranged from 35% to 50% (196–198). Although some studies report relatively high rates of improvement, the unblinded nature of these studies and the ongoing treatment of many patients limit interpretation of these results. In addition, potential adverse events range from personality changes, seizures, and hydrocephalus to transient mania and mild transient side effects such as urinary dysfunction. The recent development of less invasive (DBS) and non-invasive (TMS) procedures makes it harder to consider ablative neurosurgery as an alternative for highly treatment-resistant or intractable OCD. For the time being, DBS and ablative neurosurgical treatment for OCD should be performed only at sites with expertise in both OCD and these treatment approaches.

C. DISCONTINUATION OF ACTIVE TREATMENT

Successful medication treatment should be continued for 1–2 years before considering a gradual taper by decrements of 10%–25% every 1–2 months while observing for symptom return or exacerbation. Successful ERP should be followed by monthly booster sessions for 3–6 months, or more intensively if response has been only partial.

Four double-blind SRI discontinuation studies studied different SRIs, used different designs (e.g., length of observation and method of placebo substitution), and had different relapse definitions. These methodological differences have been associated with widely varying reported rates of relapse or discontinuation for insufficient clinical response after double-blind switch to placebo, ranging from 89% within 7 weeks to 24% within 28 weeks (80, 199–201). An open discontinuation study also reported significantly higher 6-month, 1-year, and 2-year relapse rates for the patients whose SRI treatment was discontinued (177). Thus, rates of relapse appear to be increased after discontinuation of SRI treatment but cannot be precisely specified. Given these observations, discontinuation of pharmacotherapy should be carefully considered, and for most patients, continued treatment of some form is recommended.

A review of CBT studies consisting of ERP (202) concluded that about three-quarters of patients receiving ERP (with and without concomitant medication) were doing well at a mean follow-up of a little more than 2 years after the index treatment course. The studies' methodological limitations make this finding inconclusive. In addition, the relapse definition utilized in this review differs from those used in the SRI studies, precluding comparison of relapse rates.

A multi-site study (123) found that responders to intensive ERP (with or without concomitant clomipramine) had a significantly lower relapse rate and longer time to relapse after treatment discontinuation than responders to clomipramine alone (67). Post hoc analyses generally supported these findings, albeit with substantial variability in observed relapse rates (203), depending on the specific definition of relapse.

Together, these data suggest that the response to CBT consisting of ERP may be more durable, at least in the short run, than response to some SRIs after these treatments are discontinued. However, the observed differences could be explained by other factors, including differences in the intensity of treatment before discontinuation, the rate of medication taper, the subjects studied, the length of follow-up, and the relapse criteria.

III. SPECIFIC CLINICAL FEATURES INFLUENCING THE TREATMENT PLAN

Many of the clinical features that will influence the treatment plan have been mentioned in describing the choice of a treatment setting and methods of enhancing adherence. Additional features are described below.

A. PSYCHIATRIC FEATURES

In suggesting treatments for adults, the clinician should consider the patient's response to past treatments, including the benefits and side effects, and the patient's motivation and ability to adhere to pharmacotherapy and psychotherapy. As noted, educational efforts are a standard treatment element and enhance treatment motivation. An unstable or stressful living situation diminishes the chances of successful treatment and may require concomitant interventions such as family therapy.

Assessing the patient's degree of insight is useful because it may influence willingness to cooperate with treatment. The Brown Assessment of Beliefs Scale (204) and the Overvalued Ideas Scale (OVIS) (205) provide quantitative measures. Poor insight is associated with poorer response to SRIs in most studies (71, 206) but not all (207), and poorer response to CBT in some studies (208) but not others (209–211).

Patients appear to be less likely to benefit from medications, CBT, or combined treatment (212) if their predominant or only OCD symptom is hoarding (i.e., acquiring or accumulating items such as newspapers, magazines, books, packaging, old clothing, notes, and lists that are beyond reasonable need or of little objective value). Such individuals may be less responsive to treatment than patients with other symptom patterns because they usually demonstrate less insight, less distress, and therefore less motivation for change (45, 213–217). A recent study, however, found that OCD patients who hoard responded as well to pharmacotherapy as did OCD patients with other symptom types (218). Differences in the underlying neurobiology (219) or OCD-related genetics (220) of hoarding patients compared with nonhoarding patients may also play a role. Specific treatment programs that achieve benefit with hoarding patients have been described (33, 150, 221, 222) but not tested in controlled trials. The Appendix includes a helpful Web site (San Francisco Bay Area Resource & Internet Guide for Extreme Hoarding Behavior, Clutterers Syndrome, or Pack Rat Syndrome).

1. Chronic Motor Tics

Co-occurring chronic motor tics in the absence of Tourette's disorder have been shown to decrease the likeli-

hood of response to fluvoxamine (154, 223) but not to clomipramine (224). Patients with OCD who do not respond to an SRI and have co-occurring tics may benefit from the addition of an antipsychotic drug (154, 225). Although tic onset or exacerbation during SSRI treatment is reported in isolated cases (226, 227), trials of SSRIs should not be withheld from OCD patients with co-occurring motor tics.

2. Tourette's Disorder

OCD co-occurring with Tourette's disorder can be treated with SRIs, which usually have little effect, either positive or negative, on the tic symptoms (225). When the OCD fails to respond after one or two adequate SRI trials, adding a first-generation (typical) or second-generation (atypical) antipsychotic drug in a low to modest dose may ameliorate both disorders (225).

3. Major Depression

Co-occurring major depression does not adversely affect the response of OCD to SRIs (71, 228). When the OCD responds well and the major depression does not, the clinician has many choices, none of which have been studied in large double-blind trials. As a result, it is reasonable to apply the treatment strategies outlined in APA's *Practice Guideline for the Treatment of Patients With Major Depressive Disorder* (192). These include using psychotherapies that are effective in treating depression (i.e., interpersonal psychotherapy, CBT, or short-term psychodynamic therapy), increasing the SRI dose, adding an antidepressant from another class, adding an augmenting agent, or, in patients with severe, treatment-resistant, or suicidal depression, utilizing ECT (191). In many trials of CBT (229–231), but not all (232), co-occurring major depression has been associated with a poorer OCD outcome. Severe depression clearly interferes with CBT (233). Thus, it may be useful to utilize antidepressant medication, and particularly SRIs, to treat co-occurring major depression before or during a trial of CBT.

4. Bipolar Disorder

Treatment of patients with both OCD and bipolar disorder should include measures to achieve mood stabilization before initiating treatment with agents, such as SRIs, that may induce or exacerbate hypomania or mania. Stabilizing the bipolar disorder may require a combination of medications, including lithium, anticonvulsants, and second-generation antipsychotic drugs (193). In bipolar OCD patients, SSRIs appear to be less likely than clomipramine to precipitate hypomania or mania (29). Potential drug interactions should be carefully considered when clomipramine, fluoxetine, fluvoxamine, paroxetine, or sertraline are considered for use in combination with these agents.

Episodic OCD, characterized by periods of markedly different symptom severity independent of OCD treatment, appears to be considerably more common in OCD patients with bipolar disorder (29). Thus, a history of episodic OCD should raise the psychiatrist's suspicion that co-occurring bipolar disorder may be present. Perhaps as a result of co-occurring bipolar disorder, patients with episodic OCD appear to be more likely to suffer from alcohol abuse or dependence, panic disorder, and agoraphobia (29), which will also require treatment.

5. Panic Disorder

Co-occurring panic disorder may respond to the SRI utilized to treat the patient's OCD (234) or to CBT for panic (235). When co-occurring panic disorder or a history of panic attacks is present, SRI treatment should be initiated at low doses, and the dose should be slowly titrated upward over a period of weeks, in order to avoid initiating or exacerbating panic attacks (234). Alternatively, the clinician can start an SRI at usual doses combined with a benzodiazepine at antipanic doses for the first month or so and then try tapering the benzodiazepine over a period of weeks (234).

6. Social Phobia (Social Anxiety Disorder)

Co-occurring social phobia may respond to the SRI utilized to treat the patient's OCD (236). However, in one small study, OCD patients with co-occurring social anxiety disorder experienced a poorer response to SSRI treatment than those without this condition (237). Large, double-blind, placebo-controlled studies support the effectiveness of escitalopram (238), fluoxetine (239), fluvoxamine (240), paroxetine (241), and sertraline (242), as well as venlafaxine (243) and clonazepam (244), in treating social phobia. Phenelzine, while effective, cannot be combined with SRIs because the combination is likely to cause the serotonin syndrome. Controlled trials suggest that social phobia also responds to cognitive-behavioral therapies (245).

7. Schizophrenia

The point and lifetime prevalences of obsessive-compulsive symptoms and of OCD in patients with schizophrenia are elevated (246–248). In patients with co-occurring schizophrenia, OCD or obsessive-compulsive symptoms may be present independently or may be precipitated or exacerbated by second-generation antipsychotic medications (249, 250). Clozapine is the second-generation antipsychotic most often reported to exacerbate obsessive-compulsive symptoms. However, case reports also describe this effect with risperidone (251), quetiapine (252), and olanzapine (253). Some patients with schizophrenia have insight into the irrationality of their obsessions and com-

pulsions while lacking insight into their schizophrenic delusions. In other patients, the obsessions and delusions become illogically linked, as for example when the patient believes that obsessions have been inserted into his mind by an external force or that his compulsive rituals control world events. When clinically significant OCD or obsessive-compulsive symptoms are present independently, the psychiatrist must rely on clinical judgment in formulating a treatment plan, since no large, controlled trials have been conducted.

The patient's antipsychotic regimen should first be stabilized. A review of the treatment literature (254) suggests that SRIs are usually well tolerated and can be beneficial, but isolated reports of psychotic exacerbation exist. As with all use of combination pharmacotherapies, potential drug interactions must be borne in mind. Olanzapine monotherapy has been beneficial in two case series. Adding fluvoxamine has been helpful in two open trials, as has adding fluoxetine, paroxetine, or sertraline in individual cases. Case reports suggest that low doses of fluvoxamine (75–300 mg/day) and slow upward titration are indicated (254). When a second-generation antipsychotic drug induces obsessive-compulsive symptoms, they may disappear within a few weeks. If not, treatment options include adding an SRI, switching to another second-generation antipsychotic, or attempting a trial of CBT. No controlled trials exist to guide treatment planning, but reviewing the results of published cases (249, 254) may be helpful.

8. Substance Use Disorders

Because co-occurring alcohol or substance abuse or dependence can interfere with treatment adherence and response and bring risks of drug interactions, these disorders must be treated either before or while treating the patient's OCD. Several organizations have published guidelines to aid in treatment planning (255–257).

9. Autism and Asperger's Syndrome

Repetitive thoughts and behaviors are common in children and adults with autism or Asperger's syndrome. In a recent study that carefully distinguished stereotypic behaviors and idiosyncratic interests from obsessions and compulsions, only somatic obsessions and repetition rituals were more common in adults with OCD than in adults with high-functioning autistic spectrum disorders (258). An earlier study found that, compared with adults with OCD, adults with autistic disorder had significantly more ordering, hoarding, touching, and self-injurious behaviors (259). However, about half of the autistic individuals in that study were either intellectually impaired, mute, or both. Conversely, one study reported that about 20% of OCD patients have autistic traits (260). One study found the rate of OCD to be elevated in the parents of autistic children with extensive rituals and restricted interests (261).

The SRIs have been effective in treating the repetitive thoughts and behaviors associated with autism (262). In two studies with autistic children, clomipramine was more effective than either desipramine or placebo in reducing repetitive and compulsive behaviors (263, 264). One controlled study found fluvoxamine to be significantly better than placebo for decreasing repetitive behavior and aggression in adults with autistic disorder (265). In a randomized controlled trial in children with Asperger's syndrome, CBT was effective in reducing obsessive-compulsive symptoms and other forms of anxiety (266).

10. Personality Disorders

Although the majority of studies suggest that personality disorders are common in patients with OCD (267), the literature is mixed with regard to their impact on the outcome of pharmacotherapy and of CBT. Attempts to draw conclusions are hampered by methodological problems such as small sample sizes, retrospective study design, poorly defined outcome criteria, difficulties in valid ascertainment of these disorders (268), and differing diagnostic criteria and lengths of follow-up. Some personality traits (e.g., passive-aggressive) and disorders (e.g., borderline personality disorder) have been reported to interfere with adherence to treatment (269, 270). Other traits (e.g., the odd thinking style in schizotypal personality disorder) or particular disorders (especially schizotypal personality disorder [271, 272]) have been associated with poor outcome for unclear reasons in some, but not all, studies (269, 273). Thus, the presence of a co-occurring personality disorder should not prevent a trial of CBT and/or SRIs, but rather should alert the clinician to consider whether to provide additional treatments targeting the personality disorder. Obsessive-compulsive personality disorder, which may co-occur with OCD, has, for example, been noted in case reports to respond to psychodynamic psychotherapy or individual psychotherapy with an expressive emphasis (274–276), to CBT (277), and, in a case series, to SSRIs (278). Patients with OCPD may feel threatened by a lack of control in therapy, deny negative and painful feelings, intellectualize feelings, or resist becoming "dependent" on medications or therapy. Strategies to enhance the therapeutic work with these patients include respecting the patient's defenses, helping the patient accept his or her humanness, enlisting the patient's collaboration in treatment planning, and empathizing with the patient's feelings of shame and fear (119).

11. Neurological Conditions Inducing OCD

OCD or obsessive-compulsive symptoms not meeting DSM-IV-TR diagnostic criteria can be manifestations

of a number of neurological conditions, including brain trauma, stroke, encephalitis, temporal lobe epilepsy, Prader-Willi syndrome, Sydenham's chorea, carbon monoxide poisoning, manganese poisoning, and neurodegenerative diseases such as Parkinson's disease and Huntington's disease (33, 279, 280). Treatment is first directed to the underlying neurological condition when this is possible. When OCD symptoms persist after treatment or stabilization of the underlying condition, isolated case reports suggest that treatment with an SRI and/or CBT may be of some benefit. No controlled treatment trials have been conducted in patients with OCD induced by neurological conditions.

B. DEMOGRAPHIC AND PSYCHOSOCIAL FACTORS

1. Gender

Gender does not appear to influence the likelihood of treatment response in OCD (71). However, men and women may differ in their metabolism of psychotropic medications, including those used in treating OCD (281–283). In addition, premenstrual worsening of OCD has been reported in from 20% (284) to 42% (285) of women and may influence apparent treatment responses.

2. Ethnicity

Pharmacogenetic influences on the probability of therapeutic outcomes and adverse reactions to SRIs are beginning to be reported. Differences in neurotransmitter transporter and receptor genotypes are beginning to be implicated in predicting therapeutic response. In addition, differences in the prevalence of cytochrome P450 (CYP) slow, normal, extensive, and ultra-rapid metabolizers of psychotropic medications, and hence in pharmacokinetic contributions to rates of adverse events, are being associated with ethnicity (286). For example, data indicate that 13%–23% of Asians are CYP2C19 poor metabolizers compared with 2%–5% of Caucasians, and thus should receive about 60% of the average dose of clomipramine (287). CYP2D6 poor metabolizers may require lower doses of paroxetine, which is both an inhibitor and a substrate for this enzyme (287). In the future, identifying CYP genotypes through approaches such as gene chips, may help prevent adverse responses and metabolism-related treatment failures. Although the data are too sparse to support guidelines at present, psychiatrists should remain alert for helpful information.

3. Pregnancy and Breast-Feeding

For patients wishing to become pregnant, pregnant patients, and patients who are breast-feeding, CBT alone should be considered. Deciding whether to start or stop a psychotropic drug during pregnancy or breast-feeding requires making a risk-benefit assessment without having complete information. Risks to the well-being of the fetus, the infant, and the mother occur whether medications are started or stopped, since the mother's health will influence the pregnancy outcome and postpartum infant care. A model to integrate and weigh the decision-making elements in this situation has been proposed (288). In counseling the patient and her concerned others, the physician should provide clear summaries of the available data and, if desired, aid in obtaining more detailed data (289) and provide counseling over several sessions to help the patient come to terms with the uncertainty of the risks. Two helpful Web sites are listed in the Appendix. Consultation with the patient's obstetrician-gynecologist should be offered. Because OCD patients are often quite anxious, experience doubting, and can suffer from perfectionism or a need for certainty, helping the patient and her significant other reach an informed decision may take several sessions. Documentation of the information provided and the clinical rationale for the chosen treatment approach is advisable.

OCD symptom onset during pregnancy has been reported in 13% (285) to 39% (290) of women with OCD who have been pregnant. The severity of pre-existing OCD is usually unaffected by pregnancy but has been reported to worsen in from 8% (284) to 17% (285) of women with OCD who are pregnant and to improve in 14% (285).

The available data suggest that exposure to tricyclic antidepressants (TCAs), fluoxetine, fluvoxamine, paroxetine, or sertraline does not increase rates of intrauterine death (288, 291). Whether SRI exposure decreases birth weight or increases rates of premature delivery is unclear; the data are conflicting (292). Available data do not suggest increased rates of major malformations after in utero exposure to citalopram (293) or escitalopram (294); fluoxetine, sertraline, or TCAs (288, 295); or fluvoxamine (296). However, the FDA has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations (www.fda.gov/cder/drug/advisory/paroxetine200512.htm; accessed December 13, 2005). Consequently, at the FDA's request, the manufacturer has changed paroxetine's pregnancy category from C ("Risk cannot be ruled out") to D ("Positive evidence of human fetal risk").

A neonatal behavioral syndrome that includes central nervous system, motor, respiratory, and gastrointestinal signs may occur in neonates exposed to SRIs in the third trimester. Although monitoring of exposed neonates is warranted, this behavioral syndrome is usually mild and is manageable with supportive care, and disappears by

2 weeks of age (297). Some evidence also suggests an increase in the likelihood of persistent pulmonary hypertension of the newborn when the patient receives an SSRI during the third trimester (298). Since the severity of OCD symptoms may not rapidly increase when medication is tapered, tapering the patient's SRI dose during the last weeks of pregnancy may be considered.

The very limited data regarding long-term effects of exposure throughout pregnancy to TCAs or SSRIs do not suggest an elevated risk of abnormalities in cognitive function, language, temperament, or general behavior between ages 15 and 71 months (299). In addition, one study found no evidence for developmental delay at up to 2 years of age associated with in utero exposure to TCAs, fluoxetine, sertraline, or paroxetine at varying times and for varying durations (295).

The pharmacokinetic, pharmacodynamic, and safety considerations in administering SRIs and other psychotropic drugs in pregnancy (and during breast-feeding) are reviewed elsewhere (300, 301). Although there are no data specific to OCD, increases in the SSRI dose have been needed in the early third trimester to maintain remission in major depression. The relative safety of administering first-generation antipsychotics, especially trifluoperazine and perphenazine, during pregnancy is supported by a large database (300). The data regarding second-generation antipsychotics consist only of case reports and case series totaling fewer than 100 children for any individual drug except clozapine, for which the total approaches 150 children. The FDA classifies all second-generation antipsychotics as pregnancy risk Category C ("Risk cannot be ruled out"), except clozapine, which is classified as Category B ("No evidence of risk in humans"). Benzodiazepines are apparently not associated with a significant risk of somatic teratogenesis, but the risk of neurobehavioral effects is unclear because of conflicting reports (300, 302). The reviewers recommend tapering these drugs before delivery when possible and using benzodiazepines in FDA Category C (i.e., clonazepam) or those with less potential for fetal accumulation (i.e., lorazepam and oxazepam).

The available data concerning the effects on the infant of maternal SRI ingestion during breast-feeding are derived from only a few hundred infants. The data suggest that the risk of contemporaneous, noticeable effects is quite low (300, 303). Cases of respiratory depression, hypotonia, poor feeding, irritability, and uncontrollable crying have been reported (303). There are no reports of long-term adverse effects of exposure, but in the absence of large, controlled trials or observational studies, caution remains in order. The American Academy of Pediatrics Committee on Drugs recommends that a nursing mother be informed that the infant will be exposed to maternal medications (304). No consensus exists regarding how best to measure infant exposure (305), but sertraline and paroxetine appear least likely to produce detectable or elevated infant plasma drug levels (303). Monitoring maternal or breast milk antidepressant levels is not recommended (303). Discarding the breast milk 8–9 hours after taking sertraline reduces infant exposure by a little more than 15% (305). Data helpful in evaluating the risks and benefits of taking other psychotropic drugs during breast-feeding are reviewed elsewhere (300, 306).

4. Children and Adolescents

In children and adolescents, treatment should often start with CBT or with a combination of psychotherapy and an SRI (307). Cognitive-behavioral approaches consisting primarily of ERP have been shown to be efficacious in children (308–310), and three SSRIs and clomipramine are FDA-approved for use in treating OCD in children (308, 311–313). Caution and frequent clinical monitoring are advisable when treating children and adolescents with SRIs because of the possibility of an increase in suicidal thinking or behaviors (314). However, using SRIs in treating children and adolescents with OCD or major depression may be necessary and should not be avoided when clinically indicated (315–320). As further information on the treatment of OCD in children and adolescents is beyond the scope of this guideline, the reader is referred to the practice parameter of the American Academy of Child and Adolescent Psychiatry (321).

5. The Elderly

No studies of treatment of OCD in the elderly have been published. Experience with pharmacotherapy of other psychiatric disorders in the elderly indicates that lower starting doses of medication and a more gradual approach to dose increases are often advisable in this age group. Advanced age may affect drug absorption, free drug concentration in plasma, the volume of distribution of lipid-soluble drugs (leading to an increased half-life), and renal excretion rates (322–324). Although hepatic CYP enzyme activity does not regularly diminish with age, decreases in liver mass or blood flow can lead to diminished rates of drug metabolism. For example, diminished hepatic blood flow in the elderly is associated with slower clearance of drugs metabolized by CYP3A4 (e.g., alprazolam, triazolam, sertraline, and mirtazapine). Older patients may also be more sensitive to adverse drug effects. In particular, elderly patients are more sensitive to anticholinergic effects of tricyclics, such as clomipramine, and of antipsychotic drugs. They are also more sensitive to the sedative, cardiac, autonomic, and weight-increasing side effects of these drugs. Because elderly patients are more likely to be taking medications for general medical conditions, the physician pre-

scribing anti-OCD medications will more often have to consider potential pharmacokinetic and pharmacodynamic drug interactions in these patients (73, 76, 283) (Section II.B.2).

C. TREATMENT IMPLICATIONS OF CONCURRENT GENERAL MEDICAL DISORDERS

Co-occurring medical conditions and any medications being used to treat them must be considered when the psychiatrist is choosing pharmacotherapies for OCD. In particular, the effects of kidney and liver disease on drug metabolism and the potentials for pharmacokinetic and pharmacodynamic drug interactions must be reviewed. SSRIs would be preferred over clomipramine in a) patients with epilepsy, because of lower seizure risk; b) patients with cardiac arrythmias, congestive heart failure, or blood pressure abnormalities, because of relative cardiovascular safety; and c) patients who are overweight, because of a lesser likelihood of stimulating appetite. The psychiatrist should recall that SSRIs have been associated with cases of bradycardia, hypertension, hyponatremia, bleeding (325), easy bruising, nausea, diarrhea, constipation, changes in urination, extrapyramidal symptoms, and other symptoms that can be confused with manifestations of co-occurring medical conditions or treatments (33). SSRIs may be used in patients with migraine headaches who are taking triptans (326). Moreover, they may also be used in patients with Parkinson's disease, although there are isolated case reports of worsened motor functioning (327, 328). In patients with diabetes mellitus, it is important to select second-generation antipsychotics that are least likely to affect glucose metabolism and appetite (e.g., aripiprazole and ziprasidone) (194, 329). In all cases, the potential for interactions between the patient's medical and psychiatric medications should be reviewed.

Part B

BACKGROUND INFORMATION AND REVIEW OF AVAILABLE EVIDENCE

IV. DISEASE DEFINITION, EPIDEMIOLOGY, NATURAL HISTORY, COURSE, AND GENETICS

A. DISEASE DEFINITION

The conceptualization of OCD has changed over the last two centuries (330). Obsessions, marked by preserved insight, were gradually distinguished from delusions; compulsions were distinguished from various paroxysmal, stereotyped, and impulsive behaviors. DSM-IV-TR identifies the essential features of OCD as "recurrent obsessions or compulsions (Criterion A) that are severe enough to be time consuming (i.e., they take more than 1 hour a day) or cause marked distress or significant impairment (Criterion C)" (1, pp. 456–457). The full criteria set is shown in Table 1. DSM-IV-TR describes obsessions as intrusive, persistent, unwanted thoughts, impulses, or images that give rise to marked anxiety or distress. Compulsions are physical or mental acts that the patient feels driven to perform in order to magically prevent some feared event, undo some thought, or reduce anxiety or distress. Compulsive acts—also known as *rituals*—are carried out repetitively, excessively, and usually according to rules or in a rigid manner. Compulsions are distinguished from repetitive behaviors motivated by pleasure or gratification.

The psychiatrist should differentiate between obsessions and mental rituals or compulsions, since the CBT approaches to these symptoms differ. Obsessions occur spontaneously or are evoked by a feared environmental stimulus or event and generate anxiety or distress. Mental compulsions such as counting, praying, or reviewing actions, conversations, or lists are initiated by the patient willfully, albeit sometimes reluctantly, with the aim of feeling safer or reducing anxiety or distress.

The DSM-IV (and DSM-IV-TR) diagnostic criteria differ from those in DSM-III-R in allowing a diagnosis of OCD when insight into the irrationality or excessiveness of obsessions or compulsions is severely compromised or absent. The field trial of the DSM-IV criteria (331) reported that 8% of OCD patients currently lacked insight and 5% had never had insight. Thus, DSM-IV and DSM-IV-TR incorporate a specifier, "with poor insight," and allow an additional diagnosis of delusional disorder (297.1) or psychotic disorder not otherwise specified (289.9) when obsessions are of delusional quality. The DSM-IV and DSM-IV-TR criteria also clarify that the "neutralizing thoughts" mentioned in DSM-III-R are mental compulsions, not obsessions.

The DSM-IV field trial revealed that most patients with OCD have both obsessions and compulsions (331). It was found that 96% of OCD patients had obsessions and compulsions, 2% had predominantly obsessions, and 2% had predominantly compulsions, as determined by the Y-BOCS Symptom Checklist. Patients varied with regard to which symptoms were most troubling. Clinicians rated about 49% of patients as troubled equally by obsessions and compulsions, nearly 30% as troubled predominantly by obsessions, and about 21% as troubled predominantly by compulsions.

The most common themes of obsessions are fears of contamination, of accidentally or purposely harming others, of making a significant mistake (e.g., leaving a stove on, a door unlocked, a bill incorrectly paid, throwing away something important), of committing a religious offense or moral infraction, of contracting a disease, and of being considered homosexual or committing homosexual or pedophilic acts. Hoarding, when a symptom of OCD, is not usually feared, though it may be regretted. In addition, individuals with OCD may obsess about orderliness or symmetry, lucky or unlucky numbers or colors, needing to know or to remember (e.g., everything in the news or every word in a movie), heterosexual acts, or bodily health. Obsessions are often accompanied by a feeling of doubt, uncertainty, or incompleteness that drives repetitive thought or action. Obsessive thinking is often colored by an inflated estimate of danger, an increased sense of responsibility, or a need for certainty or perfection. Reinvestigating the nature and extent of symptoms after a therapeutic alliance has been established may be helpful since patients may not reveal embarrassing symptoms in a first visit.

Because compulsions are usually performed in response to obsessions, the common themes are similar: cleaning, checking, harm avoidance, undoing, asking for reassurance or confessing, accumulating (hoarding), arranging, repeating, praying, and counting.

B. EPIDEMIOLOGY

Clinically significant OCD is not uncommon. For DSM-IV OCD, the 1-month prevalence in adults is estimated to be 0.6% (332). A large British epidemiological study utilizing ICD-10 diagnostic criteria (333) found a 1-month prevalence of 1.1%. Estimates of the 12-month prevalence in adults range from 0.6% to 1.0% for DSM-IV OCD (334, 335) and 0.8% to 2.3% for DSM-III-R OCD (336). The World Health Organization places OCD among the 10 most disabling medical conditions worldwide (337), and the National Comorbidity Survey Replication indicates that OCD is the anxiety disorder with the highest percentage (50.6%) of serious cases (338). The prevalence of DSM-IV OCD in children and adolescents is discussed elsewhere (339, 340). A meta-analysis of follow-up studies of childhood-onset OCD found that at follow-up periods of varying durations, mean persistence rates were 41% for full OCD and 60% for full or subthreshold OCD (341).

The lifetime prevalence of OCD in adults is estimated to be 1.6% (338). In contrast to the prevalence rates of DSM-IV OCD, the mean lifetime prevalence of DSM-III OCD was 2.5% across five U.S. catchment areas (336). The lifetime prevalence rates of DSM-III OCD in seven countries ranged from 0.7% (in Taiwan) to 2.5% (in Puerto Rico) (342). The differences in OCD prevalence rates between studies using DSM-III and DSM-IV criteria have been attributed to refinements in diagnostic interviews and to changes in DSM-III-R and DSM-IV that better define obsessions and compulsions and emphasize the degree of distress and impairment required for diagnosis (334). Whereas the prevalence of clinical OCD is less than 3%, up to 80% of the general population may experience intrusive, unpleasant, or unwanted thoughts (343), and about 50% may engage in ritualized behaviors (344).

The mean age at OCD onset ranges in epidemiological studies between 22 and 35 years, with at least one-third of cases beginning by 15 years (342, 345). The National Comorbidity Survey Replication reported a median age at onset of 19 years, with 21% of cases starting by age 10 (335). A second incidence peak occurs in both males and females in middle to late age in some studies (346). However, others report that onset of OCD after age 50 is unusual (280).

Males generally have earlier onset of the disorder than females, possibly contributing to a preponderance of males in most clinical samples of children and adolescents with OCD and of adults with early-onset OCD (347–349). However, several epidemiological studies of children and adolescents reported equal rates in boys and girls (339, 350). A slight female predominance is reported in epidemiological studies by age 18 years (351), a pattern

found in most adult samples (342, 345, 346). The disorder is evenly distributed across socioeconomic strata in most studies, although there tends to be a paucity of minority subjects in epidemiological and clinical studies in the United States (336).

Although the symptoms of OCD are virtually identical in children and adults, there appear to be important clinical differences between early- and late-onset OCD. Early-onset OCD has been associated with higher symptom severity ratings (347, 352), higher rates of compulsions without obsessions (348), and higher rates of clinically significant obsessive-compulsive symptoms (347, 353). It has also been associated with higher rates of co-occurring tic disorders (354, 355), ADHD, and multiple anxiety disorders (356). Childhood onset of OCD may also be associated with a somewhat greater chance of poor response to SRI treatment in adulthood (71).

There are no established environmental risk factors for OCD. The role of stressful life events (including pregnancy and childbirth) as potential risk factors for OCD still warrants further studies. However, streptococcal infection may be associated with a form of early-onset OCD that involves an abrupt onset of obsessive-compulsive symptoms and co-occurring tics, often abbreviated PANDAS for pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (357–363).

C. NATURAL HISTORY AND COURSE

The methodological limitations of available studies hinder attempts to describe the natural history and course of OCD. These limitations include differences in sampling settings; criteria for diagnosis, inclusion, improvement, or deterioration; reliance on subjects' recall of distant histories; and varying intervening treatment histories. Retrospective studies with a mean follow-up of at least 10 years and conducted before effective pharmacotherapies became available reported improvement rates of 32% to 74% (cited in reference 46). In a unique study, one psychiatrist twice evaluated 144 adult patients aged 19–52 years who had been admitted for inpatient treatment of OCD symptoms in Göteborg, Sweden, between 1947 and 1953. The first evaluations occurred between 1954 and 1956 and the second between 1989 and 1993, providing follow-ups after a mean of 47 years (46). After varying histories of treatment or no treatment, about two-thirds of the patients improved within a decade of OCD onset, and 83% by the end of the study. Nearly half (48%) experienced a "clinical recovery" (no clinically relevant symptoms for ≥5 years), but only 20% achieved a full remission (no symptoms in the previous 5 years). At the second evaluation, 80% had clinical symptoms (52%) or subclinical symptoms (obvious symptoms without distress or interference) (28%), 9% showed no improvement, and 8% had experienced a deteriorative course. Of those who were ill at the first evaluation ($n=125$), 50% had a chronic course (≥5 years of continuous symptoms of the same degree), 25% an intermittent course (≥2 episodes with symptom-free intervals), 12% an episodic course (one episode lasting <5 years), and 2% were unspecified. Relapses occurred after 20 years of remission in 17% of subjects. However, of those in remission at the first evaluation, 46% remained in remission for at least 30 years. Retrospective diagnostic evaluation indicated that 85% of the subjects met DSM-IV diagnostic criteria.

Similar statistics regarding course were reported for a cohort admitted to the University of Pisa, Italy, outpatient treatment program who met DSM-III-R diagnostic criteria and were followed up after at least 10 years of illness: 27% had an intermittent course (≥6 months of full symptom remission) [termed "episodic" by the study's authors], and 73% had a chronic course (stable or fluctuating symptoms or deterioration) (364). A U.S. study of 200 OCD outpatients meeting DSM-III-R criteria reported that 85% had a continuous course with waxing and waning symptoms, 2% had an episodic course with full remissions of ≥6 months, and 10% had a deteriorative course (365).

Only one study has involved a long-term follow-up of a community sample of OCD subjects (24). The number of OCD subjects was, unfortunately, small ($n=22$). The investigators attempted six evaluations over a 20-year period of OCD cases first diagnosed when the patients were ages 19 and 20 years in Zurich, Switzerland. The long-term outcomes were favorable. After a mean follow-up period of 12.9 years, 86% had no symptoms, 9% had symptoms and moderate distress, and only 5% met DSM-IV diagnostic criteria. Only one-third had received treatment. An epidemiological study (333) showed that individuals with OCD and other co-occurring disorders are much more likely to seek treatment than are individuals with "pure" cases (56% vs. 14%, $P<0.001$).

These studies suggest that individuals whose OCD or co-occurring disorders lead them into treatment experience a more chronic and troubling course than do individuals in all cases occurring before age 20 and ascertained through community survey. Only larger community studies can confirm or refute this impression.

D. GENETICS

1. Twin and Family Studies

The genetic epidemiology of OCD has been examined in twin and family studies but not in adoption studies (366). Both twin and family studies provide evidence that

genetic factors are involved in the transmission and expression of OCD. In two of the larger twin studies, concordance rates ranged from 80% to 87% for monozygotic twins and from 47% to 50% for dizygotic twins (367, 368). In a study with 419 twin pairs, the heritability estimate for obsessive-compulsive symptoms was 47%, suggesting that just under half of the phenotypic variation was due to genetic factors (369). In a study with 527 female twin pairs, the best-fit model suggested heritabilities of 33% and 26%, respectively, for factors roughly corresponding to obsessions and compulsions (370). By way of comparison, the heritability of panic disorder has been estimated to be approximately 43% (366, 371, 372).

Controlled family studies using adult probands have found that the lifetime prevalence of OCD is significantly higher in case compared with control relatives (10.3%–11.7% vs. 1.9%–2.7%) (373, 374). A meta-analysis of data from five family studies with adult probands found a fourfold increase in the likelihood of OCD in case versus control first-degree relatives (366).

In family studies utilizing adult probands, an early age at onset of obsessive-compulsive symptoms has been strongly associated with a more familial form of OCD (373–376). Although family studies using pediatric probands have often lacked control groups and yielded divergent results, a recent controlled family study utilizing pediatric probands found that the lifetime prevalence of OCD was significantly higher in case compared with control relatives (22.5% vs. 2.6%) (377). A second recent family study also found in case relatives, compared with control relatives, a higher age-corrected risk of OCD (22.7% vs. 0.9%) and chronic tics (11.6% vs. 1.7%) (376). In addition, first-degree relatives of probands with ordering compulsions had a significantly higher lifetime prevalence of definite and subthreshold OCD than did relatives of case probands without ordering compulsions (45.4% vs. 18.8%) (377). A similar pattern with symmetry and ordering symptoms was noted in a segregation analysis of family data (378, 379). These findings suggest that ordering compulsions along with hoarding (45) may characterize a more familial and possibly more etiologically homogeneous form of OCD.

2. Genetic Linkage and Candidate Gene Studies

A genome scan has found suggestive evidence for linkage on chromosome 9p24 (380), which has been replicated by an independent research group (381). Association studies examining candidate genes in the 9p24 region have produced mixed results, with one study finding modest association at two microsatellite markers flanking *SLC1A1* (381) and another finding no evidence of association at two single nucleotide polymorphisms (SNPs) in *SLC1A1* intron 3 (382). *SLC1A1*, which codes for the glutamate transporter EAAC1 (EAAT3), is the most promising candidate gene in the region shared by the 9p24 linkage findings and the reported 9p monosomy.

Numerous other studies have shown mixed results in examining genetic loci mainly associated with serotonergic, dopaminergic, or glutamatergic pathways or immunological processes, as functional candidate genes for OCD (e.g., see references 383–388).

Subgroups of individuals with OCD have also been examined for evidence of genetic linkages or the presence of candidate genes. For example, a genome scan focused on hoarding in affected sibling pairs with Tourette's disorder found significant allele sharing for hoarding phenotypes for markers at 4q34–35, 5q35.2–35.3, and 17q25 (220). In addition, a missense mutation described in the serotonin transporter gene appears to be associated with a complex neurobehavioral syndrome that includes OCD, social phobia, and Asperger's disorder (389).

V. REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE

A. MEDICATIONS

The following sections review evidence on the outcomes of pharmacological treatments for OCD. Unless otherwise indicated, outcomes are given for the intent-to-treat (ITT) sample with the last-observation-carried-forward (LOCF) method. ITT results inform the clinician of what outcome to expect when considering all patients exposed to a treatment. Results reported for patients who completed the study, by contrast, indicate what to expect for those exposed to completed durations of treatment. Finally, visitwise outcome results indicate likely outcomes for patients exposed to those particular durations of treatment. In considering "responder" rates reported in OCD pharmacotherapy studies, it may be helpful to keep in mind the responder rates reported in subjects in the placebo arms of such studies. As noted previously in Section II.B.6, "responders" are variously defined as subjects who experience a ≥25% or ≥35% decrease in Y-BOCS score or a CGI-I score of 1 (very much improved) or 2 (much improved), usually after 12 weeks of treatment. In one analysis of studies published before 1997, responder rates in

placebo subjects ranged from 0% to 35% (mean 15%), with later studies generally reporting higher placebo response rates (70). In the interest of brevity, the responder criteria specified above are symbolized in this section as follows: YBOCS-25%, YBOCS-35%, and CGI-I:1,2.

1. Efficacy of Clomipramine

Clomipramine is a mixed serotonin and norepinephrine reuptake inhibitor (and cholinergic and histaminic blocking agent) introduced in Europe in 1966 for treating depression. It was subsequently used for OCD and was approved by the FDA in 1989 for the treatment of OCD in the United States.

Randomized controlled studies have found clomipramine significantly superior to placebo in the treatment of OCD. However, no adequate studies have determined the minimally effective or optimal clomipramine dose. Trials directly comparing clomipramine with certain SSRIs (e.g., fluoxetine, fluvoxamine, and paroxetine) report equal effectiveness. However, in some studies the SSRIs appear to have better tolerability. Sample sizes limited the power of most of these studies to detect differences, and most studies did not include a placebo comparison group. Thus, although clomipramine is recommended for treating OCD, safety and tolerability issues favor the SSRIs.

The Clomipramine Collaborative Study (390), the first large, double-blind, placebo-controlled trial in the United States of a pharmacotherapy for OCD, was a landmark for the treatment of OCD in general, and clomipramine treatment specifically. This 10-week, double-blind, placebo-controlled, multicenter study included 260 subjects in each group. Subjects who had not received prior CBT or clomipramine and scored ≥16 on the Y-BOCS and ≥7 on the National Institute of Mental Health Obsessive-Compulsive Scale (NIMH-OC) were included. Subjects took clomipramine at a dose of at least 200 mg/day or matched placebo, with the opportunity to increase the dose to 300 mg/day. The mean Y-BOCS score in the clomipramine group decreased 40% compared with 4% in the placebo group. The YBOCS-35% responder rate in the clomipramine group (55%) far exceeded that in the placebo group (7%). In a 1-year extension (391) in a subsample (n=134) of participants in the Clomipramine Collaborative Study, OCD symptoms fell to the subclinical range in 50% of the clomipramine group, compared with 4% of the placebo group. CGI-I:1,2 responder rates for clomipramine were 50% versus 7% for placebo. Adverse reactions, however, led 17 of the 129 (13%) subjects taking clomipramine to drop out of the study.

Many additional randomized, double-blind, placebo-controlled studies or active-comparator studies support the effectiveness of clomipramine treatment of OCD (70, 392, 392b). Taken together with the findings of the Clomipramine Collaborative Study, these studies indicate that clomipramine at doses of up to 250 mg/day is an effective treatment for OCD. Adverse effects, especially anticholinergic and cardiovascular effects and weight gain, are common; however, dropout rates are not high except in one study (393). Clomipramine may elevate levels of liver transaminases, and a potential for seizures exists at doses exceeding 250 mg/day.

Several studies have compared clomipramine with other medications (also see Section V.A.2). Pigott et al. (394) compared clomipramine 250 mg/day (n=5) and fluoxetine 40 mg/day (n=6) in a small crossover trial of 10 weeks on each drug with a 4-week washout period interposed. The Y-BOCS score decreased significantly in both groups, with no between-group significant difference. Lopez-Ibor et al. (395) found no difference in Y-BOCS score decrease in an 8-week, double-blind comparison of clomipramine 150 mg/day (n=25) and fluoxetine 40 mg/day (n=30). The YBOCS-25%, but not the YBOCS-35%, responder rate was significantly higher for clomipramine. The drugs did not differ in dropout rates. This study was, however, small, had no placebo control arm, and used low doses of both medications.

A 10-week, multicenter, randomized controlled trial (396) compared clomipramine (n=34; maximum dose = 250 mg) and fluvoxamine (n=30; maximum dose=250 mg). All patients had a Y-BOCS score ≥16 at baseline, and half of the patients had had prior treatment. Improvement in Y-BOCS score was equivalent (fluvoxamine mean Y-BOCS score decrease=8.6; clomipramine decrease= 7.8). Both medications were well tolerated, but the clomipramine group experienced more sexual dysfunction. In a 10-week, multicenter, randomized controlled trial, patients scoring ≥16 on the Y-BOCS were treated with clomipramine (n=65; maximum dose=300 mg, mean=206 mg) or fluvoxamine (n=37; maximum dose=300 mg, mean= 212 mg). The drugs were equally effective (YBOCS-25% responder rates for clomipramine and fluvoxamine were 56% and 54%, respectively). Both medications were well tolerated, with no difference in dropout rates due to adverse events (397). Another 10-week, multicenter, randomized controlled trial enrolling patients scoring ≥16 on the Y-BOCS compared clomipramine (n=42; maximum dose=250 mg, mean=255 mg) with fluvoxamine (n=37; maximum dose= 300 mg, mean=201 mg). The drugs were equally effective, but fluvoxamine was better tolerated; constipation and dry mouth were problematic in the clomipramine group (398).

In a 12-week, double-blind, flexible-dose trial that included a placebo arm, clomipramine (n=99; 150–250 mg/day, mean=113 mg/day) and paroxetine (n=201; 20–

60 mg/day, mean=37 mg/day) produced equal Y-BOCS-25% responder rates (55%), which were significantly higher than that associated with placebo (35%) (393). Paroxetine was significantly better tolerated than clomipramine; withdrawal rates for treatment-emergent adverse events were 17% for clomipramine, 9% for paroxetine, and 6% for placebo. However, the placebo group had more subjects with "serious" treatment-emergent adverse events (6.1%) than did the clomipramine (2.5%) or placebo (2.0%) groups.

At least five meta-analyses have evaluated randomized, double-blind, controlled studies comparing clomipramine with SSRIs. A meta-analysis of studies comparing clomipramine and fluoxetine reported a greater effect size (Cohen's d) for clomipramine (1.84) than for fluoxetine (1.34) (399), but with fewer adverse events for fluoxetine. Dropout rates did not differ. A later meta-analysis (400) found the effect size (Cohen's d) for fluoxetine (3.45) in seven studies to be greater than that for clomipramine (3.24) in 12 studies, with a lower dropout rate for fluoxetine subjects. Using data on subjects who completed the studies, Abramowitz (69) found a modestly greater effect size (Cohen's d) for clomipramine than for certain SSRIs (effects sizes: clomipramine vs. placebo, 1.31/0.66 [clinician rating/patient rating], fluvoxamine vs. placebo, 1.28/0.37; sertraline vs. placebo, 0.37/ 1.09; fluoxetine vs. placebo, 0.68/[no patient rating done]). When the difference in side-effect profiles between clomipramine and placebo was statistically adjusted to zero, the superiority of clomipramine over the SSRIs disappeared. Eddy et al. (59) also found a greater effect size (Cohen's d) for clomipramine in analyzing 32 randomized controlled studies (18 involving clomipramine) published between 1980 and 2001, enrolling 3,500 subjects. The pre-post clomipramine effect size was 1.55; the sertraline effect size (largest among the SSRIs) was 1.36. This result must be viewed with caution because more subjects in the clomipramine trials were treatment naive, one-third of potential subjects were excluded from the studies, and only 80% completed the trials. A meta-analysis using meta-regression (effect-size modeling using least-squares regression) applied to 25 randomized controlled trials published between 1989 and 1997 found that the superiority of clomipramine over fluoxetine, fluvoxamine, and sertraline in placebo-controlled trials persisted after heterogeneity effects were controlled for (70). There was no significant difference among the SSRIs in comparisons with placebo-controlled trial results.

Several explanations have been proposed for this disparity in results between placebo-controlled and clomipramine-SSRI direct comparison studies. Abramowitz (69) suggested that clomipramine's apparent superiority may have resulted from its more obvious side effects, thus diminishing the integrity of the blind in placebo-controlled studies. Further doubt is cast on the larger effect size of clomipramine compared with the effects of the SSRIs by the fact that double-blind trials directly comparing clomipramine with fluvoxamine, fluoxetine, and paroxetine showed no difference (70), and a double-blind comparison with sertraline found sertraline more effective (401). This latter result was strongly influenced, however, by inappropriately high starting doses of clomipramine (50 mg/day), which led to a high dropout rate, and by low maximum clomipramine doses. A meta-analysis using meta-regression (70) found that age at onset, pre-trial OCD severity, date of publication, trial length, and length of single-blind pre-randomization each affected the magnitude of the treatment effect; but after these predictive factors were controlled for, clomipramine still appeared superior in comparisons across placebo-controlled trials.

Clomipramine has been compared, albeit in methodologically limited studies, with the MAOIs clorgyline and phenelzine. A small crossover study with 6-week drug treatment periods found a significant effect for clomipramine but not for clorgyline (402). A 12-week randomized trial comparing clomipramine 225 mg/day (n=16) with phenelzine 75 mg/day (n=14) found no difference, but the study was very underpowered and used nonstandard outcome measures (403).

Foa et al. (123) compared clomipramine (n=36), intensive CBT consisting of ERP (n=29), clomipramine plus intensive ERP (n=31), and placebo (n=26). In this 12-week randomized trial enrolling subjects with Y-BOCS ≥ 16, no major depression, and no prior adequate treatment with clomipramine or ERP, clomipramine was more effective than placebo. Intensive ERP combined with clomipramine was more effective than clomipramine alone but was not more effective than intensive ERP alone.

a. Intravenous Clomipramine

A few investigators have studied the effects of intravenously administered clomipramine, which produces higher immediate plasma levels by avoiding first-pass liver metabolism. However, this treatment is not available in the United States. In controlled trials, intravenous clomipramine has been shown to be superior to placebo in treatment-resistant patients (404). Pulse-loaded intravenous clomipramine was more rapidly effective than identical oral doses in a double-blind pilot study (405), but a larger study did not confirm this finding (85). Both studies reported therapeutic effects in some patients with very treatment-resistant OCD, suggesting that rapid escalation of oral doses may help such patients. Pulse-loaded intravenous clomipramine was more effective than gradually increased

intravenous clomipramine, and more rapidly so in a study in which intravenous treatment was followed by treatment with orally administered clomipramine (406).

b. Clomipramine as an Augmentation Agent

The strategy of adding clomipramine to an SSRI or vice versa is supported by expert opinion (140, 175) and several open-label trials. In a randomized, open-label, 90-day trial that compared adding clomipramine or nothing to citalopram in patients who had failed to benefit from adequate 16-week trials of both clomipramine and fluoxetine, nine of nine patients in the clomipramine augmentation group were YBOCS-35% responders, versus only one of seven patients assigned to citalopram alone (176). In patients with an inadequate response to 6 months of clomipramine 150 mg/day, Ravizza et al. (407) reported a better response and fewer side effects when sertraline 50 mg/day was added to clomipramine 150 mg/day than when the clomipramine dose was raised to 250 mg/day.

2. Efficacy of SSRIs

a. Fluvoxamine

Double-blind, placebo-controlled, and active-comparator studies indicate that fluvoxamine is significantly more effective than placebo and equal in efficacy to clomipramine and certain SSRIs (citalopram, paroxetine), although the sample size for the latter comparison was small. Compared with clomipramine, fluvoxamine showed fewer anticholinergic side effects and better tolerability. Whether the combination of fluvoxamine and CBT (particularly ERP) is more effective than CBT alone is uncertain because of methodological shortcomings in available studies.

An early double-blind, placebo-controlled trial (408) reported positive findings when 42 OCD patients—half of whom also had depressive symptoms—were randomly assigned to receive fluvoxamine (up to 300 mg/day, mean final dose=255 mg/day) or placebo for 6–8 weeks. Nine of 21 fluvoxamine patients were CGI-I:1,2 responders (mean Y-BOCS score decrease from baseline=42%) versus none in the placebo group. The majority of week 6 partial responders became full responders at week 8 of fluvoxamine treatment, suggesting that at least 8 weeks of treatment are needed to detect a full clinical response.

A 10-week, double-blind trial (409) randomly assigned 40 OCD subjects to receive fluvoxamine (up to 300 mg/day, mean maximum dose=294 mg/day) or placebo and reported a statistically significant greater improvement for fluvoxamine than for placebo on Y-BOCS and NIMH-OC but not CGI measures.

Two pivotal 10-week, multicenter, double-blind, placebo-controlled studies with identical study protocols provide convincing evidence for the therapeutic efficacy of fluvoxamine in OCD (410, 411). Subjects met DSM-III-R criteria for OCD of at least 12 months' duration and had an NIMH-OC scale score of ≥7 and a 17-item Hamilton Depression Rating Scale (Ham-D) score of ≤19. Seventy-nine (410) and 78 (411) fluvoxamine-treated subjects and 78 (410) and 80 (411) placebo-treated subjects completed the studies. Fluvoxamine was flexibly titrated to 100–300 mg/day. At week 10, the mean fluvoxamine doses were 245 and 251 mg/day, at which time the mean Y-BOCS score had fallen 21% in the fluvoxamine groups compared with 7% in the placebo groups (among patients who received at least one postbaseline rating). A statistically significant difference between the two groups was first observed at week 6. CGI-I:1,2 response (ITT) was achieved in 33% and 38% of fluvoxamine subjects compared with 9% and 15% of placebo subjects.

In the largest double-blind, placebo-controlled fluvoxamine trial (412), 253 OCD subjects were randomly assigned to receive fluvoxamine controlled release or placebo (efficacy analyses: $n=237$, 117 fluvoxamine controlled release, 120 placebo). After 12 weeks, fluvoxamine was significantly more effective than placebo on all efficacy measures, including the Y-BOCS and CGI scales. YBOCS-25% and YBOCS-35% response rates were significantly higher in the fluvoxamine group, as were remission rates (44% vs. 31% and 18% vs. 8%, with Y-BOCS score definitions of ≤16 and ≤8, respectively). Therapeutic effects were evident at week 2, which is earlier than reported in other fluvoxamine versus placebo studies, with the earlier onset of effects perhaps attributable to the higher starting dose (100 mg/day). Fluvoxamine, although having more side effects (e.g., insomnia, nausea, somnolence) than placebo, was safe and generally well tolerated.

In double-blind, active-comparator studies, fluvoxamine was superior to desipramine and as efficacious as other SRIs (clomipramine and some SSRIs); however, the lack of placebo control groups prevents calculating the net drug effect (i.e., active drug effect minus placebo effect).

In an 8-week trial (413), OCD subjects were randomly assigned to receive fluvoxamine (up to 300 mg/day, mean final dose=214 mg/day) or desipramine (up to 300 mg/day, mean final dose=223 mg/day). Forty subjects completed at least 2 weeks of treatment and were included in the efficacy analysis. The mean Y-BOCS score decreased 29% from baseline in the fluvoxamine group and was virtually unchanged in the desipramine group.

In a 12-week trial (414), 12 OCD subjects were randomly assigned to receive fluvoxamine or clomipramine (both up to 200 mg/day). For the 10 subjects who completed the study, the Y-BOCS score decreases were similar in the treatment groups; however, the small number of subjects limits the power to detect differences.

In a 10-week multicenter trial (396), fluvoxamine (up to 250 mg/day, mean final dose=200 mg/day) was as effective as clomipramine (up to 250 mg/day, mean final dose=200 mg/day). Endpoint Y-BOCS scores among the 64 randomly assigned subjects with at least one postbaseline rating did not significantly differ between the two treatment groups. Fluvoxamine produced fewer anticholinergic side effects and less sexual dysfunction than clomipramine. These findings were replicated in a subsequent 10-week study (397) that involved 79 OCD subjects randomly assigned to receive fluvoxamine (up to 300 mg/day, mean final dose=225 mg/day) or clomipramine (up to 300 mg/day, mean final dose=201 mg/day). Among the 73 subjects with at least one postbaseline rating, the percentage of Y-BOCS-25% responders in the two groups showed no difference at any time. The mean Y-BOCS score decrease was 30% in both treatment groups. The fluvoxamine group experienced fewer anticholinergic side effects.

In a large, 10-week, multicenter, double-blind trial, 227 OCD subjects were randomly assigned to receive fluvoxamine (up to 300 mg/day) or clomipramine (up to 300 mg/day) (415). Both groups experienced a marked improvement in OCD as evidenced by Y-BOCS, NIMH-OC, and CGI scores. Fluvoxamine was better tolerated primarily because troubling anticholinergic side effects were more common in the clomipramine group. In a small, 10-week, single-blind trial, 30 OCD patients were randomly assigned to receive fluvoxamine (up to 300 mg/day, mean final dose=290 mg/day), paroxetine (up to 60 mg/day, mean final dose=53.3 mg/day), or citalopram (up to 60 mg/day, mean final dose=50.9 mg/day); all patients completed the study (416). At trial endpoint the percentage of responders (with response defined as YBOCS-35% *and* a CGI-I score ≤3 [minimally improved]) showed no statistically significant differences, suggesting similar effectiveness. However, the small number of subjects in each group severely limited the power to detect differences between the drugs.

Two double-blind studies compared the efficacy of fluvoxamine combined with different forms of CBT to the efficacy of CBT alone or of CBT combined with placebo. In a combined single- and double-blind trial, 60 patients were randomly assigned to receive fluvoxamine and antiexposure therapy, fluvoxamine and ERP, or placebo and ERP (165). Pharmacotherapy (fluvoxamine up to 300 mg/day, mean dose=282 mg/day) lasted for 24 weeks. The medication was then tapered over a 4-week period and discontinued, and patients were then free to seek treatment as desired. Evaluations were conducted after 2 months of active treatment (n=50) and at the end of active treatment (6 months, n=44). Follow-up evaluations by a blinded rater were done at 1 year (n=37) and 18 months (n=33). Fluvoxamine with ERP and fluvoxamine with antiexposure therapy yielded greater reduction in rituals at week 8 than placebo with ERP, but this superiority disappeared at 1 year. By week 24, all treatments had reduced OCD symptoms, with no significant between-group differences. Fluvoxamine plus antiexposure and fluvoxamine plus ERP had more effect on depressive measures than did ERP plus placebo. However, the lack of a standard response measure (Y-BOCS), the small number of subjects in each treatment group, and varying treatments subjects received during follow-up limit interpretation of the results.

Hohagen et al. (164) randomly assigned 60 OCD inpatients to receive 10 weeks of either fluvoxamine (up to 300 mg/day, mean dose=288 mg/day) plus CBT or placebo plus CBT. The CBT consisted of therapist-aided ERP plus cognitive restructuring. In the 49 patients who completed the study, both treatments significantly reduced OCD symptoms. However, there were significantly more YBOCS-35% responders in the fluvoxamine plus CBT group (87.5%) than in the placebo plus CBT group (60%). Post hoc analyses suggested that patients with OCD and depression benefited more from fluvoxamine plus CBT than from placebo plus CBT. However, this conclusion must be viewed cautiously, as no information was given on the two groups' degree of response to prior treatments, and the analyses excluded nine subjects in order to equalize the two groups' baseline Y-BOCS scores.

Van Balkom et al. (61) randomly assigned 117 outpatients to five treatment conditions: fluvoxamine plus cognitive therapy, fluvoxamine plus self-guided ERP, cognitive therapy alone, self-guided ERP alone, or an 8-week wait-list control. Fluvoxamine was titrated to 300 mg/day, with a mean endpoint dose in the two drug groups of 197 mg/day. Pharmacotherapy lasted 16 weeks, and a naturalistic follow-up measurement was made at 6 months. Completer and ITT analyses posttreatment revealed no differences in effects (Y-BOCS, SCL-90, BDI) between the four active treatment conditions; however, this result may be due to inadequate power. Overall, 36% of subjects who completed the study were responders (Y-BOCS score ≤12 and ≥6-point improvement). No evidence was found that the combination of fluvoxamine with cognitive therapy or ERP was superior to the cognitive therapy or ERP alone. However, neither the ERP nor the fluvoxamine dosing was optimized. Moreover, because of the absence of a group treated with fluvoxamine alone and of a control group for the duration of the study, the differential efficacy of fluvoxamine, cognitive therapy, or self-guided ERP at week 16 cannot be determined.

A recent follow-up study (66) assessed 62 OCD subjects who completed controlled trials (23 treated with CBT

consisting of ERP alone, 24 with SRI alone [fluvoxamine or clomipramine], 15 with ERP plus medication) and found that most subjects showed long-term improvement following either ERP or medication treatment. The small number of patients in each group, however, limited the power to detect differences between the groups.

One fluvoxamine study supports the hypothesis that OCD with co-occurring chronic tic disorders may be a clinically meaningful subtype. An 8-week open-label trial (223) assessed the efficacy of fluvoxamine in 66 OCD patients, of whom 33 had tic disorders. Of the OCD patients with co-occurring chronic tic disorders, 21% were fluvoxamine YBOCS-35% *and* CGI-I:1,2 responders compared with 52% of the OCD patients without co-occurring chronic tics. The authors concluded that fluvoxamine monotherapy may be less efficacious in OCD patients with tics than in those free of this condition. A clomipramine study, however, found no reduction in effectiveness in OCD patients with tics (224).

b. Fluoxetine

Three randomized, double-blind, placebo-controlled studies show that fluoxetine is significantly more effective than placebo. In addition, double-blind active-comparator studies suggest fluoxetine is comparable in efficacy to clomipramine and sertraline and superior in efficacy to phenelzine. Compared with clomipramine, fluoxetine exhibited fewer side effects in one study. In other studies, fluoxetine was well tolerated, with side effects comparable to those of the comparator drugs.

Two large, randomized, double-blind, placebo-controlled studies demonstrated the effectiveness of fluoxetine in the treatment of adults with DSM-III-R OCD. In an 8-week double-blind study (417), 214 subjects were randomly assigned to receive fluoxetine 20, 40, or 60 mg/day or placebo. Fluoxetine response (defined as YBOCS-25% *and* CGI-I:1,2) rates were significantly higher in the 40 mg/day and 60 mg/day groups (48% and 47%, respectively) than in the placebo group (26%), but the response rate in the 20 mg/day group (36%) was not. In a 16-week extension, subjects who had not responded to 20 mg/day or 40 mg/day and who took fluoxetine 60 mg/day experienced a highly significant decrease in Y-BOCS scores. Fluoxetine and placebo dropout rates did not differ significantly.

A 13-week, randomized, double-blind trial (83) assessed the effects of fluoxetine 20, 40, or 60 mg/day versus placebo in 355 outpatients with OCD. At each dose, fluoxetine was significantly superior to placebo on the Y-BOCS and other efficacy measures, with statistical significance reached by week 5. The fluoxetine groups had YBOCS-35% response rates of 32%, 32%, and 35%, respectively, with a trend for greater improvement in the 60 mg/day group. The YBOCS-35% response rate in the placebo group was 8.5%. The safety and efficacy of fluoxetine in the acute treatment of OCD are further supported by open trials (418–421).

Two studies compared fluoxetine with clomipramine in the treatment of DSM-III-R OCD without using a placebo control group (394, 395). In the first study, involving crossover designs with 10 weeks of treatment, 4 weeks of drug washout, and samples of 6 and 20 subjects, fluoxetine up to 80 mg/day was as effective as clomipramine up to 250 mg/day (394). Both drugs produced a significant decrease in the Y-BOCS score, although clomipramine was associated with more adverse events. The second study, an 8-week, double-blind, randomized trial, compared fluoxetine 40 mg/day ($n=30$) with clomipramine 150 mg/day ($n=25$) (395). The two drugs appeared equally effective over this short treatment period. The YBOCS-25% responder rate, but not the YBOCS-35% responder rate, was higher with clomipramine. The discontinuation rates for adverse events were 3% for fluoxetine and 4% for clomipramine.

A 24-week, randomized, double-blind trial compared the efficacy and tolerability of fluoxetine (mean dose = 57 ± 23 mg/day) and sertraline (mean dose = 140 ± 59 mg/day) in outpatients with DSM-IV OCD (422). Equivalent and significant improvement was found at week 24 in Y-BOCS and NIMH-OC scale scores. Remission rates (defined as Y-BOCS score ≤ 11 *and* CGI-I:1,2) at weeks 12 and 24 were significantly higher for sertraline (36% vs. 22% at week 24). Subjects treated with sertraline showed an earlier improvement on some, but not all, efficacy measures. Both medications were well tolerated; rates of discontinuation due to adverse events were 14% for fluoxetine and 19% for sertraline.

A 10-week randomized trial compared fluoxetine 80 mg/day, phenelzine 60 mg/day (both doses achieved by the end of week 3), and placebo in 64 adults with DMS-III-R OCD (423). Fluoxetine was superior to placebo at weeks 6 and 10 as well as to phenelzine at week 10. Symmetry obsessions and lower baseline Y-BOCS scores were significantly more common in phenelzine responders than in fluoxetine responders; however, this post hoc analysis provides only weak evidence for a phenelzine effect in this subgroup.

The long-term treatment of OCD with fluoxetine has been examined to a limited extent. In a continuation of the 13-week, double-blind, placebo-controlled, fixed-dose fluoxetine study (83), treatment responders continued their blinded treatment, whereas nonresponders began a 24-week open-label trial of maximally tolerated doses up to 80 mg/day (81). Among acute-phase responders, all

three doses of fluoxetine (20, 40, and 60 mg/day) were associated with further Y-BOCS improvement. The acute-phase nonresponders benefited from upward dose titration, with two-thirds achieving a YBOCS-35% response. Another study assessed the efficacy and safety of 52 weeks of fluoxetine or placebo treatment in patients with DSM-IV OCD who had responded to single-blind fluoxetine for 20 weeks (201). Patients who received fluoxetine had numerically lower relapse rates compared with those who received placebo, although the difference was not significant (see Section V.E for details).

c. Paroxetine

Three double-blind placebo-controlled trials show paroxetine to be more effective than placebo acutely; an additional double-blind study shows the superiority of paroxetine relative to placebo in maintaining response over 6 months of continuation treatment. A double-blind active-comparator study suggests that paroxetine is comparable in efficacy to clomipramine. Compared with venlafaxine, the relative efficacy of paroxetine is less clear, as findings vary with the definition of treatment response. Paroxetine's tolerability is comparable to that of other SSRIs. Some evidence (424), but not all (80), suggests paroxetine is more likely to be associated with significant weight gain. Paroxetine is more likely to induce anticholinergic side effects than are other SSRIs (118, 425). It also carries a greater risk of an unpleasant withdrawal syndrome, comparable to the risk associated with venlafaxine (426).

In a 12-week double-blind trial (80), OCD patients without co-occurring major depression, tics, or Tourette's disorder were randomly assigned to receive paroxetine 20 mg/day (n=88), 40 mg/day (n=86), 60 mg/day (n=85), or placebo (n=89). A little more than half of subjects had had a prior SRI trial. Endpoint response rates (defined as YBOCS-25% *or* Clinical Global Impression–Severity [CGI-S] score decrease of ≥2 points) for paroxetine 40 mg/day (25%) and 60 mg/day (29%), but not 20 mg/day (16%), were significantly greater than for placebo (13%). In a 12-week, double-blind, flexible-dose study (427), 191 subjects were randomly assigned to receive placebo or paroxetine, with the dose increasing from 20 mg/day to 40 mg/day by week 3 and up to 50 mg/day from week 8 onward. The CGI-I:1,2 response rate was significantly greater in the paroxetine (50%) than in the placebo group (24%). A significantly greater response rate was similarly observed in subjects randomly assigned to receive 12 weeks of flexibly dosed paroxetine 20–60 mg/day (mean dose= 37 mg/day) (n=201) or placebo (n=99) (393). More than half (55%) of the paroxetine subjects were YBOCS-25% responders compared with 35% of placebo subjects. The active comparator, flexibly dosed clomipramine (150–250 mg/day, mean dose=113 mg/day), produced the same responder rate as paroxetine.

A 12-week, randomized, double-blind, flexible-dose study (172) comparing paroxetine with venlafaxine found no significant difference in YBOCS-35% responder rates for paroxetine at doses up to 60 mg/day (44%) (n=76) and venlafaxine at doses up to 300 mg/day (37%) (n=75), although the YBOCS-25% responder rate was higher for paroxetine (66%) than for venlafaxine (49%). When the medication for nonresponders in this study was switched to the alternative medication in a double-blind fashion, a higher YBOCS-25% responder rate was observed for paroxetine (56% [15/27]) than for venlafaxine (19% [3/19]) (171).

Long-term effectiveness of paroxetine has been observed in one study. Responders to paroxetine in a 12-week double-blind study and its 6-month open-label, flexible-dose extension phase (N=105) were randomly assigned to receive 6 months of double-blind paroxetine or placebo (80). Relapse was defined as a return to the baseline Y-BOCS score or an increase of ≥1 point in the CGI-S score for more than one visit. Subjects assigned to placebo had a significantly higher relapse rate (59%) than those assigned to paroxetine (38%). The mean time to relapse was 29 days in the placebo group and 63 days in the paroxetine group.

d. Sertraline

Two double-blind, placebo-controlled trials demonstrated the efficacy of sertraline in treating OCD. In double-blind active-comparator studies, sertraline appeared comparable in efficacy to fluoxetine. Sertraline was superior in efficacy to clomipramine (although methodological shortcomings influenced the latter comparison) and, in subjects with co-occurring depression, was superior to desipramine. Finally, in an open-label trial, subjects who responded to 1 year of treatment with sertraline experienced further small but noticeable decreases in symptoms when treatment was extended to 2 years.

In a 12-week, randomized, fixed-dose trial (82), subjects were assigned to sertraline 50 mg/day (n=80), 100 mg/day (n=81), 200 mg/day (n=80), or placebo (n=84). Sertraline at doses of 50 mg/day and 200 mg/day was significantly superior to placebo with regard to change in Y-BOCS, NIMH-OC, CGI-S, and CGI-I scores, but at 100 mg/day sertraline was only superior in terms of the NIMH-OC, probably because of the high dropout rate (33%) in this group. At endpoint, CGI:1,2 responder rates were 39% for sertraline and 30% for placebo. A 12-week, double-blind, randomized study of flexibly-dosed sertraline 50–200 mg/day (mean maximum dose at endpoint =

165±55 mg/day) found the drug (n=86) more effective than placebo (n=81) with regard to change in Y-BOCS, NIMH-OC, and CGI-S scores (428). The CGI-I:1,2 responder rate was numerically but not significantly higher for sertraline (41%) than for placebo (23%).

In a 24-week, double-blind, randomized, flexible-dose comparison of sertraline 50–200 mg/day (mean endpoint dose=140±59 mg/day) (n=77) versus fluoxetine 20–80 mg/day (mean endpoint dose=57±23 mg/day), the differences in CGI-I:1,2 responder rates (60% and 60%) and remission (defined as CGI-I:1,2 *plus* Y-BOCS<12) rates (36% vs. 22%) were not significant (422).

A 16-week double-blind study compared sertraline and clomipramine 50 mg/day for 4 weeks followed by flexible increases in dose to 200 mg/day (mean final dose=132 mg/day for sertraline and 101 mg/day for clomipramine) (401). The sertraline group had significantly greater improvement as measured by the Y-BOCS, NIMH-OC, and CGI-S. Inappropriately high starting doses of clomipramine (50 mg/day), producing a high dropout rate and low maximum clomipramine dose, strongly influenced the comparative result. Among subjects treated for at least 4 weeks, the two drugs produced equal results, but the mean final clomipramine dose was relatively low. The Y-BOCS-35% responder rates were 72% for sertraline and 65% for clomipramine.

In another double-blind, flexible-dose study (429), OCD patients with co-occurring depression were randomly assigned to receive sertraline 50–200 mg/day (mean endpoint dose=160±50 mg/day) or desipramine 50–300 mg/day (mean endpoint dose=194±90 mg/day). Sertraline (n=79) was more effective than desipramine (n=85) in bringing about "robust improvement in OCD symptoms" (Y-BOCS score decrease ≥40%).

A second completed year of continued treatment with open-label sertraline flexibly dosed from 50 mg/day to 200 mg/day was associated with a mean decrease in Y-BOCS scores from about 12 to about 9 in 38 subjects (430) who had been CGI-I:1,2 responders in a 1-year, fixed-dose, double-blind study (431).

Finally, after 1 year of single-blind treatment, sertraline responders rarely relapsed over 28 weeks regardless of whether they were maintained on flexibly dosed sertraline (50–200 mg/day) (3/108, or 3%) or switched over 2 weeks to placebo (5/113, or 4%) (200) (see Section V.E. for details).

e. Citalopram

A double-blind, placebo-controlled trial showed citalopram to be more effective than placebo, with a trend for greater efficacy and more rapid response at a higher dose. Several open trials suggest efficacy for citalopram in individuals whose OCD has not responded to other SRIs. In addition, several open-label trials suggest comparable efficacy to other SRIs. The active isomer in citalopram, escitalopram, is now marketed as a separate SSRI in the United States.

In the only double-blind, placebo-controlled, randomized trial, 12 weeks of treatment with fixed-dose citalopram 20 mg/day (n=102), 40 mg/day (n=98), or 60 mg/day (n=100) produced higher YBOCS-25% response rates (57%, 52%, and 65%, respectively) than did placebo (n=101) (37%) (432). There were trends for the highest dose to be associated with a more rapid response.

A small open-label trial suggests that citalopram (n=11; mean dose=51 mg/day) and paroxetine (n=9; mean dose=53 mg/day) bring about similar YBOCS-35% responder rates (40% and 45%, respectively) in inpatients (416). The response rate to fluvoxamine (n=10; mean dose=290 mg/day) (60%) was numerically but not statistically significantly higher. An open-label, random-assignment, flexible-dose study utilizing a blinded rater found no significant difference in YBOCS-35% responder rates to 12 weeks of citalopram 40–60 mg/day (n=23) (48%), fluvoxamine 200–300 mg/day (n=83) (55%), clomipramine 150–250 mg/day (n=37) (48%), or paroxetine 40–60 mg/day (n=16) (50%) (433).

An open-label trial of citalopram flexibly dosed from 20 mg/day to 60 mg/day (mean final dose=46 mg/day) reported that 22 of 29 (76%) patients who completed 24 weeks of treatment experienced a ≥50% decrease in Y-BOCS score (434). Among 18 patients who completed 16 weeks of citalopram (20 mg/day for 2 weeks, then 40 mg/day) after nonresponse to two or three adequate, 6-month SRI trials (Y-BOCS decrease <25% and score ≥21), 14 (78%) were CGI-I:1 responders (435). A shorter 12-week trial (176), using the YBOCS-35% definition, reported a lower responder rate: only one of seven (14%) subjects who had failed to benefit (Y-BOCS score decrease < 35%) from fluoxetine (≥20 mg/day for ≥12 weeks) and from clomipramine (≥150 mg/day for ≥12 weeks) responded to citalopram (20 mg/day for 2 weeks, then 40 mg/day).

A single case report described a patient whose OCD was unresponsive after 3 months of citalopram 80 mg/day but subsequently responded to 160 mg/day, which was well tolerated over several months (436). Intravenous citalopram (unavailable in the United States) was well tolerated in one study at doses of 20–80 mg/day and may have a faster onset of action than oral citalopram (437).

Escitalopram was as effective as paroxetine for OCD in a European multicenter double-blind, active-comparator trial (437a) and was superior to placebo in preventing OCD relapse in a second large European double-blind trial (437b).

f. Venlafaxine

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that does not have an FDA indication for OCD. A small, double-blind, placebo-controlled trial with venlafaxine was negative, but several open-label trials showed robust responses in OCD symptoms at doses of at least 225 mg/day. In addition, double-blind active-comparator studies suggest venlafaxine is comparable in efficacy to clomipramine and perhaps to paroxetine. Venlafaxine has been generally well tolerated.

In the only double-blind, placebo-controlled trial (438), 30 OCD patients were randomly assigned to receive placebo or venlafaxine (up to 225 mg/day) for 8 weeks. At endpoint, there were no statistically significant differences in response, although there was a trend for greater response in the venlafaxine group. The study's small sample size, short trial length, low venlafaxine dose, and lack of standard outcome measures (Clinical Global Impression, ratings of avoidance) severely constrain interpretation.

In a 12-week, double-blind, active-comparator study (172), 150 OCD patients were randomly assigned to receive venlafaxine XR (up to 300 mg/day) or paroxetine (up to 60 mg/day). Full response was defined as a Y-BOCS score decrease of ≥50% and partial response as a decrease of ≥35%. An ITT LOCF analysis demonstrated no significant differences in responder rates (full response: 24% venlafaxine vs. 22% paroxetine; partial response: 37% venlafaxine vs. 44% paroxetine). Only a small percentage of patients (5%) dropped out because of adverse effects. The study's methodological limitations include the absence of a placebo control group and venlafaxine doses not exceeding 300 mg/day. In addition, the venlafaxine group had undergone more unsuccessful medication trials.

Nonresponders (Y-BOCS decrease <25%) in this study (n=43) were treated for 12 additional weeks with the alternative medication (171). A significantly higher proportion of those whose medication was switched to paroxetine (56%, 15/27) were YBOCS-25% responders compared with those whose medication was switched to venlafaxine XR (19%, 3/16). However, the small sample size, the lack of a placebo control group, and a less stringent response criterion are methodological limitations in this second study.

In a 12-week double-blind trial (173), 73 OCD subjects were randomly assigned to receive venlafaxine (225–350 mg/day, mean dose=265 mg/day) or clomipramine (150–225 mg/day, mean dose=168 mg/day). Visitwise and LOCF analyses at study end revealed no statistically significant difference between the groups in YBOCS-35% *and* CGI-I:1,2 responder rates (visitwise responder rates: venlafaxine 36% vs. clomipramine 50%; LOCF responder rates: venlafaxine 35% vs. clomipramine 43%). The investigators concluded that venlafaxine at these doses may be as effective acutely as clomipramine, with fewer side effects. However, confidence in these results is again limited by the lack of a placebo control group, the small size of the study, and by the relatively low mean clomipramine dose.

An open, naturalistic, retrospective study examined treatment results for 39 OCD patients (29 who were "nonresponders" [undefined] to one or more SRI trials) after treatment for a mean of 18 months (range 1–56 months) with venlafaxine up to 450 mg/day (mean final dose=230 mg/day) (439). At study end, 69% of subjects entering the study were CGI-I:1,2 responders. Of note, 76% of the "nonresponders" to one or more SRI trials, and 82% of the "nonresponders" to two or more SRI trials were sustained responders. Venlafaxine even at the higher end of the dosing range was well tolerated.

An 8-week open-label trial in which 12 OCD patients were treated with venlafaxine 150–300 mg/day reported responder rates of 75% (YBOCS-35%) and 35% (CGI-I:1,2) (440) without substantial side effects. A 12-week open-label trial utilizing venlafaxine 150–350 mg/day in 10 OCD patients reported responder rates of 30% (YBOCS-35%) and 40% (CGI–I:1,2), with a more robust response in treatment-naive patients (441). Marazziti (442) reported five patients whose OCD was resistant to SSRIs who improved (Y-BOCS, Ham-D, and other clinical evaluations) for at least 1 year with venlafaxine 150–225 mg/day.

3. Implementation of SRIs

Available trial data suggest that higher SSRI doses produce a somewhat higher response rate and somewhat greater magnitude of symptom relief (79–82) (Table 5).

Among nonresponders, raising the dose of an SSRI is associated with enhanced response (Table 6). The literature does not allow specification of the chance of response as a function of the number of previously failed adequate SRI trials. Attempts to interpret the clinical trial data are limited by differences in the number of failed trials in patients included in a given study, by absence of information about the number of failed adequate trials, by differences in the definition of "failed," and by the small, highly selected samples. However, clinical experience suggests that patients who do not respond to one SRI may still respond well to another (Table 7). With SRIs, response rates to a second trial are close to 50% but may fall off as the number of failed adequate trials increases. A switch to venlafaxine at doses of 225–350 mg/day is also supported by active-comparator trials and open-label studies that suggest its effectiveness in treating OCD.

TABLE 5. Effects of Higher Selective Serotonin Reuptake Inhibitor (SSRI) Doses in Fixed-Dose Trials on Obsessive-Compulsive Disorder (OCD)

Drug	Study	Response Definition	Response Achieved	Dose 1	Dose 2	Dose 3
Fluoxetine	Tollefson et al. 1994 (83)	YBOCS ↓ ≥35% (mean ↓)	Week 13 LOCF	20 mg 32% (3.4 points)	40 mg 32% (4.6 points)	60 mg 35% (5.9 points)
Citalopram	Montgomery et al. 2001 (432)	YBOCS ↓ ≥25% (mean ↓)	Week 12 LOCF	20 mg 57% (8.4 points)	40 mg 52% (8.9 points)	60 mg 65% (10.4 points)
Sertraline	Greist et al. 1995 (431)	YBOCS ↓ in mean score	Week 12 LOCF	50 mg ~6.8 points	100 mg ~5.7 points	200 mg ~7.5 points
Paroxetine	Hollander et al. 2003 (80)	YBOCS ↓ in mean score	Week 12 LOCF	20 mg 4.1 points	40 mg 6.4 points	60 mg 7.3 points

Note. LOCF=last observation carried forward; YBOCS=Yale-Brown Obsessive Compulsive Scale.

4. Other Antidepressants

a. Monoamine Oxidase Inhibitors

There is only very weak support for the use of MAOIs in OCD. In one small, double-blind, placebo- and fluoxetine-controlled study, the Y-BOCS score decrease for subjects completing a 10-week trial of phenelzine 60 mg/day (n=17) was not significantly greater than for those completing placebo treatment (n=18), in contrast to the Y-BOCS score decrease produced by fluoxetine 80 mg/day (n=19) (423). In a post hoc analysis, the authors suggested that symmetry obsessions might be a strong predictor of phenelzine "response" (undefined). In a blinded, 12-week, random-assignment, open-label comparison of phenelzine 75 mg/day (n=12 completers) and clomipramine 225 mg/day (n=14 completers), with both doses reached by week 5, no significant difference was found on either the Maudsley Obsessional-Compulsive Inventory (MOCI) or a nonstandard scale (403). The absence of a placebo group, use of nonstandard rating scales, and small sample size limit this study's evidentiary weight. A case series (443) and isolated case reports add only minimal evidence of the effectiveness of MAOIs. The presence of severe anxiety or panic attacks or of symmetry obsessions has been a positive predictor in some case reports.

TABLE 6. Effects of Raising the Dose of Selected SSRIs in Nonresponders

	Initial Phase		Continuation Phase		
Drug	Duration	Dose	Duration	Dose	Responder Rate[a] (n)
Fluoxetine[b]	13 weeks	20 mg	26 weeks	60 mg	80%[c] (8/10)
				80 mg	46%[c] (15/33)
		40 mg		60 mg	20%[c] (1/5)
				80 mg	53%[c] (17/32)
		60 mg		80 mg	50%[c] (15/30)
Sertraline[d]	16 weeks	200 mg	12 weeks	200 mg	34%[e] (10/29)
				377 mg	52%[e] (11/21)

[a]Response defined as a decrease of ≥25% on the Yale-Brown Obsessive Compulsive Scale.
[b]Tollefson et al. 1994 (83).
[c]Last observation carried forward.
[d]Ninan et al. 2006 (84).
[e]Completers.

TABLE 7. Chance of Responding to the Next Serotonin Reuptake Inhibitor (SRI) After Failure to Benefit From the Previous SRI

Study	Drug Switched to and Dose	Outcome Measurement	Response Definition	Responders	
				Drug Naive	Drug Experienced
Rasmussen et al. 1997 (168)	Sertraline 50–200 mg	Week 12	CGI-I=1,2	53% (*N*=293)	33% (*N*=172)
Goodman et al. 1997 (87)	Fluvoxamine 50–300 mg	Week 10	CGI-I=1,2	50% (*N*=126)	19% (*N*=31)
Ackerman et al. 1998 (169)	Fluoxetine 20, 40, 60 mg	Week 13	YBOCS ↓ ≥35%	42% (*N*=83)	11%–27%[a] (*N*=19, 59)
Ravizza, cited in Hollander et al. 2002 (170)	Venlafaxine 225–350 mg Clomipramine 150–225 mg Citalopram 40–60 mg	Week 12	YBOCS ↓ ≥35%	—	38% (*N*=8) 27% (*N*=11) 11% (*N*=9)
Koran et al. 2006 (85)	Clomipramine 100–250 mg	Week 13	YBOCS ↓ ≥35%	—	34% (*N*=32)
Denys et al. 2004 (171)	Paroxetine (P) 60 mg Venlafaxine (V) 300 mg	Week 12	YBOCS ↓ ≥25%	—	V→P 56% (*N*=27) P→V 19% (*N*=16)

Note. CGI-I=Clinical Global Impression–Improvement; YBOCS=Yale-Brown Obsessive Compulsive Scale.
[a]Eleven percent if previously treated with SRIs alone; 27% if previously also treated with CBT.

The side-effect burden of MAOIs can be significant and includes cardiovascular problems and weight gain, as well as potentially severe drug-drug interactions and dietary restrictions associated with nonselective MAOIs or high-dose selective MAOIs (444, 445). This burden, combined with the relative lack of evidence for MAOI efficacy, argues against the use of these medications except in severely ill OCD patients who have failed most or all first-line treatments and most second-line treatments.

b. Tricyclic Antidepressants

Limited investigations of TCAs other than clomipramine have found no evidence for their efficacy in treating OCD.

A randomized controlled trial comparing nortriptyline, clomipramine, and placebo with eight subjects in each treatment group found that clomipramine, but not nortriptyline, was superior to placebo in reducing interview-based ratings of OCD severity (446). However, there was no significant difference in effectiveness between clomipramine and nortriptyline.

In a placebo-controlled trial that divided OCD subjects into a "high depression" group (Beck Depression Inventory [BDI] score ≥ 21) and a "low depression" group (BDI score ≤20), imipramine (mean dose=233/mg/day) reduced depression over 6 weeks in the highly depressed patients (*n*=37) but did not affect the obsessive-compulsive symptoms in either depressed group (447).

In another study, 38 patients were divided into moderately and mildly depressed groups according to their Beck Depression Inventory scores (232). One half of each group received imipramine and the other half received placebo for 6 weeks followed by 3 weeks of daily CBT consisting of ERP and then 12 weekly sessions of supportive psychotherapy. Although imipramine improved depressive symptoms in the depressed patients, it did not affect obsessive-compulsive symptom severity. ERP reduced OCD symptom severity, but imipramine did not potentiate ERP effects. Response of OCD to therapy did not differ in moderately depressed versus mildly depressed patients.

c. Trazodone

Case reports and case series (448) suggest that trazodone at doses of at least 250 mg/day may warrant a trial in OCD patients who have not responded to first- and second-line treatments. In one case series (*N*=5), augmentation of an SSRI with trazodone 300–600 mg/day was helpful in alleviating OCD and anxiety as well as sleep disturbance,

TABLE 8. Results of Second-Generation Antipsychotic Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder (Double-Blind, Placebo-Controlled Trials)

	Medication	Mean Final Dose (mg/day)	Final Dose Range (mg/day)	Active Drug: Responders[a]/Total (*N*)	Percentage of Responders, Drug/Placebo
Carey et al. 2005 (458)[b]	Quetiapine	169	25–300	8/20	40%/48%
Fineberg et al. 2005 (459)	Quetiapine	215	50–400	3/11	27%/10%
Denys et al. 2004 (158)	Quetiapine	—[c]	200–300	8/20	40%/10%
Erzegovesi et al. 2005 (157)	Risperidone	0.5	0.5	5/10[d]	50%/20%
McDougle et al. 2000 (155)	Risperidone	2.2	1–4	9/20	45%/0%
Hollander et al. 2003 (156)	Risperidone	2.3	NA	4/10	40%/0%
Bystritsky et al. 2004 (159)	Olanzapine	11.2	5–20	6/13	46%/0%
Shapira et al. 2004 (460)[b]	Olanzapine	6.1	5–10	9/22	41%/41%

[a]Unless noted otherwise, responder is defined as patient having ≥25% decrease in Y-BOCS score from baseline to endpoint.
[b]Short prior SRI trial prior to antipsychotic augmentation.
[c]No mean final dose provided.
[d]Responder is defined as patient with ≥35% decrease in Y-BOCS score.

gastrointestinal distress, and sexual dysfunction (449). However, a 10-week, double-blind, placebo-controlled trial with 11 patients who completed the trazodone trial (mean dose= 235 mg/day) and 6 patients who completed the placebo trial found no evidence of efficacy (450). Nevertheless, the trial may have been too short (6 weeks at ≥250 mg/day) with too small a sample to allow definitive conclusions. If trazodone is used, sedation is likely to be a limiting side effect, and torsades de pointes has been reported on rare occasions (451). Males must be warned of the risk of priapism, which may occur in from 1/1,000 to 1/10,000 men (451).

5. Antipsychotics

a. Monotherapy

Few studies have examined the efficacy of antipsychotics as monotherapy for OCD, and the available evidence does not support such use. An early study (452) examined chlorpromazine in a mixed population of patients (those with "psychoneuroses or personality disorders with some symptoms of an obsessive or compulsive type") and did not use standardized assessment instruments. Case studies using haloperidol were inconclusive (e.g., references 453 and 454), although a case report described an OCD patient who responded well to loxapine (455).

An open 10-week trial involving 12 OCD patients examined the possible efficacy of clozapine 300–600 mg/day (456). The patients had not responded (Y-BOCS score decrease ≥35% or score <16 and a CGI-I:1,2) to prior SRI trials. Two patients dropped out because of side effects (i.e., sedation and hypotension). Among the 10 patients who completed the study, none had a response to the trial; the mean Y-BOCS reduction was 10%. The authors concluded that clozapine is ineffective as monotherapy in patients who have not responded to prior SRI treatment.

Most recently, Connor et al. (457) examined the efficacy of aripiprazole in eight OCD patients over 8 weeks. Seven patients took aripiprazole at a dose of 10–30 mg/day, but two dropped out due to side effects (i.e., akathisia, nausea). Among the five completers, three experienced a Y-BOCS decrease of ≥30%; two subjects were rated much or very much improved. The authors concluded that some patients may benefit from aripiprazole monotherapy. However, the small sample and open-label design preclude strong conclusions.

b. Augmentation

In the many OCD patients who have either no response or a partial response to SRI treatment, antipsychotic medication has been used to augment treatment with an SRI. Randomized, placebo-controlled augmentation trials of both first-generation (haloperidol) and second-generation (risperidone, olanzapine, quetiapine) antipsychotic medications have yielded response rates in the range of 40% to 55% within 4–6 weeks (Table 8).

Other controlled trials did not find significant differences between antipsychotic and placebo augmentation (458–460); however, methodological limitations in these studies likely contributed to the negative findings. In two of these studies (458, 460), in which SSRI monotherapy was limited to 8 weeks, the failure of active drug to sepa-

rate from placebo was probably due to a high rate of response to continued SSRI monotherapy in the placebo augmentation group. One 16-week, double-blind, placebo-controlled trial (459) found no significant difference between quetiapine (mean final dose=50–400 mg/day) and placebo. Again, the dosing may have been low.

The long-term effects of antipsychotic augmentation have not been systematically studied. A retrospective chart review (160) found that 15 of 18 patients (83%) who responded to antipsychotic augmentation relapsed within 1 year after the antipsychotic was discontinued. Thirteen of the 15 who relapsed did so by the eighth week after discontinuation.

Many questions about antipsychotic augmentation in OCD remain unanswered, including the optimal dose for each of the agents, their long-term tolerability, and the reasons some patients benefit but others do not. In addition, the relative efficacy of the different agents remains to be examined.

c. Haloperidol

In the first double-blind, placebo-controlled study of antipsychotic augmentation (154), 34 patients with OCD resistant to 8 weeks of fluvoxamine (defined as less than a YBOCS-35% decrease or a score ≥16 and not having a CGI-I:1,2) were randomly assigned to receive 4 weeks of adjunctive haloperidol (n=17) or placebo (n=17). Adjunctive haloperidol (initiated at 2 mg and increased to a maximum of 10 mg/day) was significantly more effective than placebo. Eleven of the 17 haloperidol patients responded versus none of the patients receiving placebo, but akathisia requiring propranolol treatment was common. Response was defined as 1) YBOCS-35% *and* score <16; 2) CGI-I:1,2; and 3) consensus of the treating clinician and two of the primary investigators. Of the 11 responders, 7 met all three criteria, and 4 met two criteria. All 8 subjects with co-occurring tics responded to haloperidol, versus 3 of 9 without tics. No subject with tics responded to placebo. The authors concluded that OCD patients with a chronic tic disorder might benefit from adjunctive haloperidol but that it should not be used indiscriminately because of the risk of tardive dyskinesia.

A 9-week, double-blind, placebo-controlled, crossover study compared 2 weeks of adjunctive treatments with risperidone 1 mg/day, haloperidol 2 mg/day, or placebo in 16 patients with Y-BOCS scores of ≥16 after at least 12 weeks of therapeutic SRI doses (461). Haloperidol augmentation, but not risperidone augmentation, reduced the Y-BOCS score significantly more than did placebo augmentation. Both drugs were significantly better than placebo at reducing Y-BOCS obsession scores. Four subjects dropped out of the study before receiving neuroleptic treatment. Of the 12 subjects (75%) who completed the risperidone arm, 5 (42%) discontinued haloperidol for adverse events. The low dose of risperidone that was used constrains interpretation of the study results (see Section V.A.5.d).

d. Risperidone

Three double-blind, placebo-controlled studies, albeit of modest size, and several open-label studies support the safety and effectiveness of risperidone augmentation of SRI treatment of OCD. McDougle et al. (155) randomly assigned 36 patients whose OCD was resistant to 12 weeks of SRI treatment (<YBOCS-35% decrease or a score ≥16 and CGI-I:1,2) to 6 weeks of adjunctive risperidone (n=20) or placebo (n=16). Risperidone was initiated at 1 mg/day, and the dose was increased by 1 mg weekly. The mean final risperidone dose was only 2.2 mg/day (SD=0.7 mg/day; range=1–4). Among patients who completed the trial (risperidone, n=18; placebo, n=15), risperidone was significantly superior to placebo (Y-BOCS reduction: 32% for risperidone; 9% for placebo). Nine (50%) of the 18 patients who completed the risperidone trial were responders compared with none of the 15 patients who completed the placebo trial. Response was defined as 1) YBOCS-35% *and* score <16; 2) CGI-I:1,2; and 3) consensus of the treating clinician and two of the primary investigators. There was no difference in outcome between OCD patients with and without co-occurring tic disorder or schizotypal personality disorder. Risperidone was well tolerated, with mild transient sedation being the most prominent adverse effect; one risperidone patient dropped out in the first week because of intolerable insomnia.

In a smaller controlled study (156), 16 OCD patients who had "failed" (i.e., no more than minimally improved) at least two 12-week SRI trials were randomly assigned to receive 8 weeks of adjunctive risperidone (n=10) or placebo (n=6). Risperidone was started at 0.5 mg/day, and the dose was increased by 0.5 mg weekly to a maximum of 3 mg/day; the mean risperidone dose was 2.25 mg/day (SD=0.86), with no difference between responders and nonresponders. In the ITT sample, the risperidone group had a numerically larger mean Y-BOCS score decrease (25%) than the placebo group (5%). Four of 10 (40%) risperidone patients and none of six (0%) placebo patients were YBOCS-25% responders. Three subjects discontinued (risperidone, n=1; placebo, n=2) because of unsatisfactory clinical response. Risperidone was generally well tolerated; only four risperidone patients experienced side effects (i.e., sedation, dizziness, dry mouth).

A randomized controlled trial (157) examined the efficacy of adding risperidone 0.5 mg/day versus placebo in OCD patients who had either responded or not re-

sponded to their first SRI trial (12 weeks of fluvoxamine, maximum dose=300 mg/day, final doses not provided). Responders (defined as those with YBOCS-35% *and* CGI-I:1,2) and "nonresponders" were then randomly assigned to receive added risperidone 0.5 mg/day or placebo for 6 weeks. Among the 39 patients completing the trial, added risperidone significantly reduced OCD symptoms in the 10 fluvoxamine nonresponders but not in the 9 fluvoxamine responders (Y-BOCS reduction for fluvoxamine nonresponders: risperidone 26%, placebo 7%; Y-BOCS reduction for fluvoxamine responders: risperidone 4%, placebo 28%). Among the fluvoxamine nonresponders, 5 of 10 (50%) risperidone patients and 2 of 10 (20%) placebo patients became YBOCS-35% responders. The study's limitations include the small sample size, the potential for ceiling effects in the fluvoxamine responders, the low dose of risperidone, and the lack of information about whether the treatment groups received similar fluvoxamine doses prior to augmentation.

e. Olanzapine

The safety and effectiveness of adjunctive olanzapine in OCD have been examined in two randomized, placebo-controlled trials and several open-label trials. Bystritsky et al. (159) randomly assigned 26 OCD patients who had not "improved" (undefined) after at least two 12-week SRI trials and at least one ERP trial to 6 weeks of adjunctive olanzapine (n=13) or placebo (n=13). OCD patients with current co-occurring Axis I disorders were excluded. The mean olanzapine dose was 11.2 mg/day (SD=6.5; range: 5–20 mg/day). In the ITT sample, adjunctive olanzapine was significantly superior (Y-BOCS reductions: olanzapine 17%; placebo 2%). Six (46%) of 13 olanzapine patients were YBOCS-25% responders compared with none in the placebo group. Two olanzapine patients (15%) discontinued because of the side effects (sedation: n=1; weight gain: n=1).

Shapira et al. (460) randomly assigned OCD nonresponders (<25% decrease) or partial responders (YBOCS-25% but score ≥16) after 8 weeks of fluoxetine (40 mg/day in 42 subjects, 20 mg/day in 1 subject), to 6 weeks of adjunctive olanzapine (n=22), or placebo (n=22). Olanzapine was started at 5 mg/day, and the dose was increased to a maximum of 10 mg/day. Both treatment groups improved significantly, with no significant difference between them; the proportions of responders were similar (YBOCS-25%=41% for both groups; YBOCS-35%=23% for olanzapine, 18% for placebo). The authors concluded that adding olanzapine was not superior to extending the 8-week fluoxetine monotherapy trial. However, as they noted, the patients were unlikely to have attained full benefit from the SSRI before the olanzapine trial began, thus obscuring any olanzapine effect. Olanzapine patients gained a mean of 2.8 (±3.1) kg compared with 0.5 (±1.8) kg for placebo patients.

f. Quetiapine

The safety and effectiveness of quetiapine augmentation of SRI treatment in OCD have been evaluated in three randomized, double-blind, placebo-controlled trials; one randomized, single blind, placebo-controlled trial; and several open-label studies.

Denys et al. (158) randomly assigned 40 OCD patients without co-occurring diagnoses who were unresponsive (Y-BOCS decrease<25%) after at least two SRI trials (at maximum tolerated dose for 8 weeks) to receive adjunctive quetiapine (n=20) or placebo (n=20) for 8 weeks. Quetiapine was started at 50 mg/day, and the dose was increased, following a fixed dosing schedule, to a maximum of 300 mg/day. In the ITT sample, adjunctive quetiapine was significantly superior to placebo (Y-BOCS reduction: quetiapine 32%; placebo 7%). Eight (40%) quetiapine patients were responders (defined as YBOCS-35% *and* CGI-I:1,2), compared with only two (10%) placebo patients. The most common side effects of quetiapine were somnolence (95%), dry mouth (55%), weight gain (30%), and dizziness (30%).

Carey et al. (458) randomly assigned 41 patients who had not responded (defined as not CGI-I:1,2 or not YBOCS-25%) after 12 weeks of SRI treatment to 6 weeks of flexibly dosed adjunctive quetiapine (n=20) or placebo (n=21). The mean final quetiapine dose was 169 (±121) mg/day. Both quetiapine and placebo led to a significant reduction in mean Y-BOCS scores (Y-BOCS reduction: quetiapine 27%; placebo 26%). Responder (defined as CGI-I:1, 2 and YBOCS-25%) rates were 40% and 48% for quetiapine and placebo, respectively. Two quetiapine patients dropped out because of severe sedation, and 75% complained of sedation (vs. 33% of placebo patients). Quetiapine augmentation was no more effective than placebo, but the study was limited in that patients had received their maximum SRI dose for only 6 weeks before randomization.

Fineberg et al. (459) randomly assigned 21 adult OCD patients with minimal response (defined as <25% Y-BOCS decrease) after 12 weeks of an SRI at the maximum tolerated dose, to receive either adjunctive quetiapine (n=11; mean final dose=215 mg/day, range=50–400 mg/day) or placebo (n=10). After 16 weeks of augmentation, there was no difference in the ITT sample between the two groups (Y-BOCS reduction: quetiapine 14%; placebo 6%). Three of 11 quetiapine-treated patients were YBOCS-25% responders compared with 1 of 10 placebo patients. The authors suggested that exclusion of co-occurring Axis I disorders and tic disorders may have led to their negative findings.

In a single-blind placebo-controlled study (462), 27 OCD patients with no response to at least one 12-week SRI trial (defined as no more than minimal improvement, a Y-BOCS score of ≥18, and agreement of three of the authors) were randomly assigned to receive adjunctive quetiapine (n=14) or placebo (n=13) for 8 weeks. Of the 14 patients randomly assigned to 50–200 mg/day of quetiapine, 10 (71%) experienced improvement (defined as Y-BOCS decrease ≥30%), in comparison to none of the placebo patients. Nine quetiapine-treated patients reported side effects (nausea, n=6; sedation, n=3; dizziness, n=1). The study's main limitation was the single-blind design.

g. Other Antipsychotic Agents

Double-blind, placebo-controlled studies are not available for ziprasidone or aripiprazole. Published case reports weakly suggest that ziprasidone augmentation of SRI pharmacotherapy may be effective (463). A small (n=8), open-label, 8-week, flexible-dose study of aripiprazole (10–30 mg/day) monotherapy reported that three subjects (38%) experienced a 30% or greater decrease in Y-BOCS score (457).

6. Other Agents

a. Adrenergic Agents

Pindolol, a beta-blocker and serotonin$_{1A}$ (5-HT$_{1A}$) presynaptic receptor antagonist, increases serotonergic transmission through its effect on the presynaptic 5-HT$_{1A}$ receptor. It has been suggested that pindolol can be given once or twice daily for augmentation in the treatment of psychiatric disorders (464). In OCD, small studies have produced mixed results regarding its possible efficacy as an augmentation agent. An 8-week, double-blind, placebo-controlled trial examined pindolol augmentation of fluvoxamine in 15 patients (180). No differences between the two treatment groups were noted either in symptomatic response or in the latency of response to fluvoxamine. A double-blind, placebo-controlled trial enrolled 14 patients with DSM-IV OCD who had not responded to paroxetine and at least two other SRIs (179). Augmentation with pindolol 2.5 mg three times daily was associated with significant decrease in the Y-BOCS score after the fourth week of treatment. The greatest improvement was noted in the ability to resist compulsions. No group differences were found in pulse rate or blood pressure. An open-label study found beneficial therapeutic effects from combining pindolol and a serotonergic antidepressant, but only after tryptophan was added (465). Another open-label study found that one of eight patients with treatment-resistant OCD responded to pindolol augmentation (466).

A double-blind crossover comparison trial with 6-week drug periods found clonidine (maximum dose = 1.0 mg/day) ineffective in 28 patients with DSM-III-R OCD (467).

b. Benzodiazepines

Evidence for beneficial effects of benzodiazepines as monotherapy for OCD is primarily limited to case reports with clonazepam and alprazolam. For clonazepam, negative results from a double-blind, placebo-controlled trial (468) and an open trial (469) cast serious doubt on the positive results of a double-blind, multiple-crossover trial (467). In the latter study, effectiveness seems to have necessitated doses that were poorly tolerated and produced serious adverse events. Modest doses of benzodiazepines may relieve anxiety and distress in OCD without directly diminishing the frequency or duration of obsessions or compulsions. However, case reports have noted an onset of action within 1–3 weeks. Among patients with histories of substance abuse or dependence, benzodiazepine use may aggravate symptoms and should be prescribed cautiously (234, 255). Thus, given their limited evidence for efficacy, benzodiazepines cannot be recommended as monotherapy for OCD, except in those rare individuals who are unable or unwilling to take standard anti-OCD medications.

c. Buspirone

Small and methodologically limited studies provide inconsistent results regarding the possible effectiveness of buspirone 60 mg/day as monotherapy and no substantial evidence of its effectiveness as an augmenting agent.

A 6-week double-blind comparison of buspirone titrated to 60 mg/day (n=10) and clomipramine titrated to 250 mg/day (n=10) suggested equal effectiveness (470). In a 4-week, double-blind, placebo-controlled, crossover trial (n=13), however, buspirone was no better than placebo (471). In addition, an 8-week open trial of buspirone at a dose of 60 mg/day for the last 5 weeks of the trial resulted in virtually no decrease in the mean Y-BOCS score of the 10 subjects who completed the study (472). However, these trial durations were too short to allow a robust test of buspirone's possible effectiveness.

In a small (n=14), 10-week, double-blind, placebo-controlled trial, which involved a 2-week placebo lead-in followed by 10 weeks of buspirone augmentation, buspirone did not differ from placebo, although 29% (4/14) of buspirone subjects experienced a YBOCS-25% response (473). A 6-week, double-blind, placebo-controlled trial of buspirone 60 mg/day as an augmentation of fluvoxamine was negative, but this study assessed the efficacy of buspirone augmentation in patients with treatment-resistant OCD (<35% decrease in Y-BOCS score and rated "unimproved" by the investigators) rather than in partial responders for whom further improvement was sought (474).

d. Inositol

Inositol, a precursor in the phosphatidylinositol cycle, has been studied in two double-blind, placebo-controlled, crossover studies (as monotherapy in one and as an augmenting agent in the other) and an open augmentation trial. Inositol appears to be well tolerated. In addition, the data weakly suggest that inositol may benefit a minority of OCD patients but do not support a recommendation that it be routinely tried.

In a double-blind, crossover study, inositol (18 gm/day) and placebo were administered for 6 weeks in each condition in 13 subjects free of major depression and with variable responses to SSRIs (475). There was a small but significantly greater decrease in the Y-BOCS score in the inositol condition (5.9 points) compared with the placebo condition (2.8 points). A double-blind, placebo-controlled, crossover augmentation study with 6 weeks in each condition and no washout between conditions found no difference in Y-BOCS score decrease between inositol and placebo in the first drug condition, but the study groups were small (six inositol and four placebo) (476). Subjects had been taking a stable SRI dose for at least 8 weeks before randomization but showed greater improvement in the study's first 6 weeks than in its second 6 weeks, regardless of which blinded drug was administered first. In an open study (477), inositol (18 gm/day) was added for 6 weeks in 10 subjects who had been rated minimally improved on the CGI-I after 12 weeks or more of stable SSRI treatment. Mean Y-BOCS scores fell significantly from 23.6 (±4.4) to 17.6 (±4.6), but only three subjects (30%) achieved CGI-I scores of much improved.

e. Lithium

Case reports suggest that lithium monotherapy may deserve further study in trials that utilize an adequate serum level (≥0.6 mEq/L) and an adequate duration of treatment (≥10 weeks). However, findings from an 8-week, double-blind, crossover augmentation study (n=16) with a mean serum level of 0.54 mEq/L (478) and a 4-week, double-blind, placebo-controlled, augmentation trial (n=10) with a mean serum level of 0.77 mEq/L (479) were negative. The 4-week lithium treatment period in these studies may have been too short to fully evaluate lithium's potential utility as an augmentation agent in OCD. The utility of lithium in the treatment of co-occurring bipolar disorder is clearly established (193).

f. Mirtazapine

A study combining an open-label first phase with a double-blind discontinuation phase suggests that mirtazapine may be effective for OCD in patients who have not received SRI treatment or have not responded to only one adequate SRI trial (174). However, the small sample size (15 treatment-naive patients and 15 not responding to exactly one adequate SRI trial) makes these results suggestive rather than strong evidence for mirtazapine's effectiveness. Significant weight gain was observed in more than 30% of patients in the first 12 weeks of treatment. A small pilot study provides slight additional support (480). Additional double-blind, placebo-controlled trials utilizing a parallel groups design are indicated.

g. Other Medications

A case series (481) and a double-blind, placebo-controlled crossover study (182) suggest that once-weekly oral morphine sulphate 30–45 mg may be useful as an augmentation strategy for resistant OCD. In the double-blind study, 7 of 23 subjects (30%) experienced a YBOCS-25% response to morphine versus none in the placebo condition. In addition, a small (n=8), 6-week, open-label study found evidence for the effectiveness of tramadol monotherapy 254±119 mg/day in the six patients who completed at least 2 weeks of treatment (183). The dose-limiting side effect was sedation.

Some anticonvulsants (valproate, oxcarbazapine, carbamazepine, gabapentin, topiramate) have been reported to help individual patients either as monotherapy or as augmentation agents. A small (n=9), 8-week, open-label carbamazepine trial (482) and a small case series (n=5) (483) each reported only one positive response. A 6-week open-label study of gabapentin augmentation (mean dose=2520 mg/day) in five patients who had a partial response to fluoxetine suggested some benefit (484), but a 6-week, double-blind, placebo-controlled, crossover trial of gabapentin 3600 mg/day added to fluoxetine found no benefit (485). An open case series reviewing at least 14 weeks of topiramate augmentation (mean daily dose=253 mg) in 16 patients who had a partial response or no response to SRI treatment reported 11 of 16 (68.8%) CGI-I:1,2 responders. The mean time to response was 9 weeks (486).

L-Tryptophan 3–9 gm/day combined with nicotinic acid 1 gm two times daily and pyridoxine 200 mg two times daily was reported to be beneficial in early case reports that predated modern diagnostic criteria and measurement instruments (487, 488). However, some patients became violent. Adding L-tryptophan at doses exceeding 1–2 gm/day to an SRI can induce the serotonin syndrome.

D-Amphetamine 30 mg, studied in a single-dose, double-blind, placebo-controlled trial, was associated with a significant decrease in self-rated symptoms about 6 hours after the dose, independently of effects on mood (184). D-Amphetamine had an acute anti-OCD effect in 11 of 12 subjects (92%). With placebo, neither the self-ratings nor the blinded observer's ratings decreased significantly. Two

patients continued D-amphetamine at a dose of 10–20 mg/day for "several weeks" with continued response. In a small (n=11), double-blind, placebo-controlled, crossover study of single doses of methylphenidate 40 mg and D-amphetamine 30 mg, both taken orally, the latter drug was associated with a significantly greater reduction in OCD symptom rating than was placebo (185). Five of the 11 subjects (45%) had a ≥50% decrease in their OCD scores after D-amphetamine, two (18%) after methylphenidate, and only one (9%) after placebo. In both studies, the decrease in OCD symptoms was independent of mood effects. Open-label methylphenidate, 40 mg once orally, produced no significant effect on OCD or mood 4 hours later in a small study (n=13), although four patients had a 50% decrease in an OCD rating scale score (489). Case reports exist of OCD benefit after treating co-occurring attention-deficit disorder with stimulants. The presence of tics or Tourette's disorder does not contraindicate the use of stimulants to treat ADHD co-occurring with OCD, although methylphenidate appears to be better tolerated in this situation than D-amphetamine (490).

Hallucinogens have been reported to alleviate OCD in individual cases (491, 492). Since hallucinogens are not a practical treatment modality or recommended, studies of safer serotonin$_{2A,C}$ (5-HT$_{2A,C}$) receptor agonists may be warranted.

Ondansetron 1 mg three times daily was associated with a significant decrease in Y-BOCS scores in a small (n=8), 8-week, open-label study (493).

St. John's wort (450 mg of 0.3% hypericum two times daily), a weak serotonin-reuptake inhibitor, was associated with CGI-I:1,2 response in 5 of 12 (42%) subjects in a 12-week open-label trial (494). However, a 12-week, flexible-dose, placebo-controlled trial enrolling 60 subjects found St. John's wort to be no better than placebo (181). In addition, St. John's wort predisposes to photosensitivity and interacts with anti-HIV medications (495), cyclosporin (496, 497), and birth control pills (498), among other medications (499).

Bupropion titrated from 150 mg/day to 300 mg/day after 2 weeks had no mean effect on Y-BOCS scores in an open trial involving 12 patients (500). However, 2 patients were YBOCS-25% responders; 4 patients "improved," with a mean Y-BOCS decrease of 31%, but 8 patients experienced a worsening of symptoms, with a mean Y-BOCS increase of 21%.

A 12-week open-label study adding riluzole 50 mg two times a day to SSRIs and other augmenting medications reported that 7 of 13 (54%) patients with treatment-resistant OCD were YBOCS-35% responders (501). However, these results must be viewed cautiously because ratings were not blinded, other augmenting medications were present, and prior treatment regimens were stable for only 4 weeks before riluzole was added. Riluzole was well tolerated, although one patient experienced an asymptomatic increase in liver enzyme (ALT) to a level more than nine times normal, which decreased despite continued treatment.

B. OTHER SOMATIC THERAPIES

Somatic therapies used in the treatment of OCD include deep brain stimulation and other forms of neurosurgery, transcranial magnetic stimulation, and electroconvulsive therapy. Plasmapheresis has been investigated only in childhood OCD. None of these therapies are considered first-line treatments for OCD, and their use is limited to patients with treatment-resistant OCD.

Specific descriptions of the criteria used to establish treatment resistance and to determine eligibility for surgical treatments (stereotactic lesion procedures and DBS) in OCD patients have been published elsewhere (152, 502–504).

Data regarding treatment of OCD with these somatic therapies are quite limited, and there is an understandable absence or paucity of double-blind trials; as a result, no definitive conclusions can be drawn. The majority of available reports are case series and open-label trials. Although stereotactic lesion procedures have a more abundant database (197) than the other somatic therapies in patients with treatment-resistant or intractable OCD, the cost, irreversibility, and lack of a clear relationship between specific anatomic lesions and successful outcomes continue to limit their use.

1. Transcranial Magnetic Stimulation

Findings of the four published trials of repetitive TMS (rTMS) are inconsistent, perhaps because the studies differed in design, stimulation sites, duration, and stimulation parameters. The available results and the technique's non-invasiveness and good tolerability should encourage future research, but the need for daily treatment may limit the use of TMS in practice.

In a TMS study of possible frontal lobe involvement in OCD (505), 12 OCD patients (6 patients with past or current major depression) were randomly assigned to receive one session of active right-side or left-side or sham (occipital) rTMS. Blinded raters made ratings during the stimulation and 30 minutes and 8 hours after the session. Compulsive urges, but not obsessions, decreased significantly, and positive mood increased moderately, with right lateral prefrontal rTMS (during stimulation and 30 minutes and 8 hours after stimulation), but not after left rTMS or occipital rTMS. Stimulation was well tolerated, with two

patients reporting mild headache after stimulation. Although the report was not intended as a treatment study (only one administration per anatomical site was used), methodological limitations include the treatment duration, lack of Y-BOCS outcome measures, small sample size, and the lack of a control group. Another non-treatment TMS study reported altered cortical excitability in subjects with OCD compared with controls (506).

A 6-week trial (three sessions per week) (507) found no advantage for low-frequency right rTMS ($n=10$) over sham stimulation ($n=8$). No dropouts were reported, and side effects, consisting of headache and cognitive difficulties, were modest and transient. The use of a relatively nonfocal, teardrop-shaped coil limits the interpretation of the results.

In a 10-session, single-blind, 2-week trial (508), 12 patients with treatment-resistant OCD were randomly assigned to receive active right-side or left-side rTMS. Ten subjects taking medications were maintained on a constant dose for 8 weeks prior to and during the study. Evaluations after 2 weeks of stimulation and 4 weeks later showed significant reduction in obsessions and compulsions in both groups, with no significant difference between right and left stimulation. Four patients (two receiving left and two receiving right rTMS) had a clinically significant improvement (Y-BOCS reduction >40%); one patient relapsed but responded somewhat to repeat treatment. No dropouts were reported, and stimulation was well tolerated, with three patients reporting headache. However, interpretation is limited by the absence of a placebo control group and the presence of concurrent pharmacotherapy.

In an open-label trial (509), 10 treatment-resistant patients (5 with OCD, 3 with Tourette's syndrome, and two with both) received low-frequency rTMS for 2 weeks. Medication doses were stable for at least 12 weeks before and throughout rTMS and the follow-up period. Eight patients completed the study; no dropouts due to side effects were reported. CGI scores decreased significantly at the end of the first and second weeks of treatment, with benefit maintained at the 1-month and 3-month follow-ups. Three of the five patients with pure OCD had a clinically significant improvement, with a >40% reduction in Y-BOCS scores, and two Tourette's patients had a complete remission at the second week. Six subjects (60%) had clinical improvement that persisted at 3-month follow-up. The study was limited by the open design and small sample size.

2. Electroconvulsive Therapy

The literature on ECT in treatment-resistant OCD includes a case series and several individual cases, with some reported degree of effectiveness. However, the frequent Axis I comorbidity among subjects, lack of standard outcome measures, absence of blinded trials, need for repeated anesthesia, and the side effects of ECT preclude it from being considered for treatment-resistant OCD uncomplicated by co-occurring conditions (191).

The case series (190) describes a retrospective study of 32 patients with DSM-III-R treatment-resistant OCD (19 not depressed and 13 depressed; 14 with primarily checking rituals, 13 with primarily cleaning rituals, and four with both) who received ECT between 1979 and 1991. The patients were treated with bilateral frontotemporal ECT (average three to five seizures per session over 2–3 weeks) and were evaluated 2 days before treatment and at 5 days and 6 and 12 months after the end of treatment. Comparison of baseline scores (Beck Hopelessness Scale, Maudsley Obsessional-Compulsive Inventory) with data 5 days after treatment yielded highly significant pre-post paired t test results ($P<0.001$) that were still significant at 6 months posttreatment. However, by 12 months only the MOCI scores remained significantly different from those prior to ECT. In addition, methodological limitations include the absence of blinded ratings and standard outcome measures, the use of medications during the long-term follow-up, and the presence of co-occurring depression in a significant proportion of patients (13/32). Furthermore, the number of seizures per session is not considered standard ECT treatment (191).

In addition, several single case reports (510–514) suggest possible efficacy of ECT in treatment-resistant OCD. However, the unblinded ratings, frequent Axis I comorbidity (schizophrenia, depression, Tourette's disorder), and differing ECT parameters limit the confidence that can be placed in the findings.

3. Deep Brain Stimulation

Two small, double-blind trials and several case reports have investigated the efficacy of DBS in OCD. Given the preliminary promising results in treatment-resistant OCD, the procedure's reversibility and adjustability in comparison with ablative neurosurgery, and the absence to date of serious adverse events, DBS deserves investigation in severe, treatment-resistant OCD. Nonetheless, DBS is an invasive procedure, and the risks of brain hemorrhage, infection, and new onset of seizures must be kept in mind (195).

The first report (515, 516) concerns six subjects with OCD refractory to various antiobsessional treatments and to CBT (Y-BOCS ≥ 30, GAF ≤ 45, both for a minimum of 5 years) who were treated with DBS. Quadripolar electrodes were implanted bilaterally in the anterior limbs of the internal capsules with a double-blind stimulation-off

condition representing the placebo condition throughout the 21 months of evaluation. Four patients completed a blinded crossover trial (i.e., stimulator on for 3 months and stimulator off for 3 months, or vice versa, in random order). Three were YBOCS-35% responders during the stimulation-on condition, with CGI-I scores much improved. Responders reported clinically meaningful improvement in the first week of stimulation. Side effects included fatigue and memory disturbances. The persistence of the effect for at least 21 months argues against a placebo effect. Patient 5 received a different electrode placement, one in each dorsomedial thalamic nucleus and one in each internal capsule (517). The dorsomedial thalamic nucleus did not seem as effective a target for this patient, who was also considered a nonresponder with longer-term internal capsule stimulation. Patient 6 experienced a major improvement (more than 50% decrease in postoperative tests) in his aggressive, intrusive thoughts and mood when stimulation was turned on.

One small trial enrolled four subjects with DSM-IV OCD who did not respond to at least four antiobsessional medications and CBT (Y-BOCS ≥ 25; GAF ≤ 44) (518). The patients, who had been following stable medication regimens for at least 6 weeks before surgery and during the blinded phase of the study, received DBS with quadripolar electrodes placed stereotactically in the anterior limb of each internal capsule; stimulation-off was the control. The double-blind study consisted of four consecutive 3-week periods (in an alternating on-off design), followed by an open phase in which stimulation, medication, and CBT were adjusted to optimize response for up to 1 year. During the double-blind phase, two of the four patients showed clinically meaningful responses but one of these patients also responded during periods without stimulation. One subject experienced mood elevation in response to stimulation. Positron emission tomography (PET) scans showed orbitofrontal deactivation only in the two patients with a positive clinical response. Side effects included tingling, nausea, and diarrhea. Beneficial effects appeared over variable times, ranging from 3 weeks to several months.

In addition, four recent case reports of open-label DBS (519–522) suggest the efficacy of DBS in treatment-resistant patients with OCD. In a recent case-series report (523), three of four patients with severe OCD and anxiety disorders who received DBS in the shell of the right nucleus accumbens experienced significant reduction in severity of symptoms.

4. Neurosurgical Stereotactic Lesion Procedures

Neurosurgical treatment for psychiatric disorders has a long and controversial history. Today this approach—including cingulotomy, capsulotomy (also performed via radiosurgery and known as "gamma-knife" capsulotomy), subcaudate tractotomy, limbic leucotomy, central lateral thalamotomy/anterior medial pallidotomy—is a highly selective treatment performed for relatively few patients with severe, treatment-refractory affective, anxiety, or obsessive-compulsive disorders (197). The availability of reversible and adjustable DBS may lead to a decrease in the use of ablative neurosurgical procedures. However, these procedures still represent a potentially efficacious alternative for a few carefully selected patients with very severe OCD.

In view of the changes in neurosurgical techniques in the last decade, only trials using these advanced techniques with adequate numbers of patients and specified inclusion criteria and outcome measures are reviewed.

A prospective unblinded study of bilateral anterior capsulotomy in 15 subjects with treatment-refractory OCD (mean duration = 18.1 ± 5.6 years; mean total Y-BOCS score = 29.7) observed positive results at 1 and 12 months postsurgery: at 12 months, the mean Y-BOCS score decrease was 39%, with 53%, 29%, and 17% of the patients experiencing a 33% decrease, 50% decrease, and 66% decrease in Y-BOCS score, respectively (524). No cognitive deficit was evident in neuropsychological screening tests. Complications were observed in three case subjects: one with transitory hallucinations, one with a single epileptic seizure, and one who developed a progressive behavior disorder (not further specified) that became permanent.

In an unblinded study (525) enrolling 44 subjects with DSM-III-R OCD refractory to at least three SRIs trials, at least one SRI augmentation trial, and a trial of CBT (Y-BOCS ≥ 25, GAF ≤ 60, both for ≥ 5 years), one or more cingulotomies (electrodes positioned in each cingulate gyrus with magnetic resonance imaging [MRI] stereotactic guidance) were performed. Follow-up evaluations were carried out a mean of 32 months after neurosurgery. At the first follow-up (a mean of 6.7 months after the first cingulotomy), the mean Y-BOCS score decrease was 20%; 5 patients (11%) met full responder criteria (YBOCS-35% *and* CGI-I:1,2), and 4 patients (9%) met partial responder criteria (either YBOCS-35% or CGI-I:1,2 *or* this degree of improvement not attributed to cingulotomy). At the 32-month follow-up, the mean Y-BOCS score decrease was 29%, with 32% of patients classified as responders and 14% as partial responders. At the most recent follow-up for the 18 patients who received multiple cingulotomies, 5 (28%) were responders and 2 (11%) were partial responders. These results suggest that cingulotomy may benefit some patients with severe treatment-refractory OCD. Although 20% of patients reported at least one adverse effect after cingulotomy (e.g., memory disturbances, apathy, urinary disturbances), only 2 patients (5%)

reported enduring sequelae (i.e., seizure disorder and hydrocephalus).

Fourteen subjects with treatment-refractory and medically intractable OCD were evaluated up to 12 months after bilateral anterior cingulotomy (526). At the 6- and 12-month follow-ups, the mean Y-BOCS scores decreased 29% and 36%, respectively, with 4 of 14 (29%) and 6 of 14 (43%) having a response (defined as YBOCS-35% *and* CGI-I:1,2). No significant changes in cognitive functions or memory were reported at the 12-month evaluation compared with preoperative scores. Adverse effects (headache, insomnia, weight-gain/loss) persisted no more than 3 months after cingulotomy.

In a retrospective unblinded study, 15 subjects with treatment-refractory OCD were followed up for approximately 1 year after bilateral cingulotomy (527). Four of the 15 patients were YBOCS-35% responders. However, only one had sustained benefit lasting more than 1 year. Minor postoperative symptoms included headache, nausea/vomiting, and urinary incontinence, which resolved after several months. Postoperative MRIs revealed no clear relationship between lesion location and significant clinical improvement.

The efficacy of limbic leucotomy was evaluated in a small unblinded study of 21 subjects, of whom 15 had treatment-refractory OCD and 6 had refractory major depression (528). Patients were evaluated after a mean of 26 months. Five of 12 OCD patients (42%) with physician ratings were rated responders (defined as physician-rated CGI-I:1,2), and 8 of the 13 (62%) OCD patients with self-ratings rated themselves as responders (defined as PGI-I:1,2). One OCD patient, who had a history of a suicide attempt, died by suicide after the surgical procedure. Minor postoperative symptoms of headache, low-grade fever, and nausea/vomiting were common but generally lasted less than 48 hours. Among the 21 subjects, transient postoperative somnolence and apathy were noted in 29% and 24% of patients, respectively. These results are comparable to those in the limited previous reports regarding limbic leucotomy in intractable OCD (529).

C. PSYCHOTHERAPIES

1. Exposure and Response Prevention

Historically, CBT for OCD has been divided into two forms: 1) CBT that relies primarily on behavioral techniques, such as ERP (57), and 2) CBT that relies primarily on cognitive therapy techniques, such as identifying, challenging, and modifying faulty beliefs (530, 531). Certain variants of exposure therapy routinely include some informal cognitive therapy techniques (e.g., a discussion of fear-related thoughts and beliefs), and many variants of cognitive therapy include behavioral experiments, which can be similar to exposure techniques. Therefore, these two forms of CBT, as administered in treatment trials, often overlap. In clinical practice, these two forms are often combined.

Studies that have examined CBT consisting of ERP for adults with OCD are reviewed in this section (see also reference 532).

a. Randomized Controlled Trials Comparing ERP With a Nonactive Treatment

Several randomized controlled trials have examined whether ERP is superior to a nonactive treatment. Although the studies used different variants of ERP (e.g., therapist-supervised or self-controlled exposures), different formats (e.g., individual sessions vs. group therapy), different intensity (e.g., frequency and length of sessions per week), and different control groups, all studies concluded that ERP is efficacious for the treatment of adults with OCD.

Several early controlled studies reported that ERP was superior to progressive muscle relaxation (PMR) (e.g., see references 533, 534). These studies were limited by their small samples and the lack of standard diagnostic and outcome measures.

A 12-week trial compared the effectiveness of random-assignment individual ERP ($n=31$), group ERP ($n=30$), or PMR ($n=32$), which was included as an attention control condition (132). Subjects were free of major depression and Axis II disorders and were treatment naive. Individual ERP was delivered in 1-hour sessions two times a week; group ERP consisted of 2-hour sessions two times a week delivered in groups of 10. In both cases, treatment consisted of exposure (imaginal and in vivo) and response prevention. In those subjects who completed treatment, both individual and group ERP were superior to PMR but not to each other in reducing OCD and depressive symptoms (Y-BOCS score reduction in subjects who completed the study: 40% for individual; 46% for group; 9% for PMR). However, group ERP took much less staff time. Patients receiving either individual or group treatment maintained their gains at 6-month follow-up; however, whether patients received additional treatment during follow-up is unclear.

In a 3-week trial in which all patients completed the study, 18 patients were randomly assigned to receive either ERP ($n=9$) or anxiety management ($n=9$) (535). Both treatments involved about 15 hours of therapy. ERP consisted of graded exposure to feared situations and ritual prevention both in sessions and as homework. Anxiety management consisted of breathing retraining, PMR, and problem solving. ERP was significantly superior to anxiety management for both OCD and depressive symptoms

(e.g., Y-BOCS: 62% reduction for ERP; 6% increase for anxiety management). During the study, five patients continued SRIs that had brought "no improvement" for at least 12 months. Study limitations include the small sample, lack of independent raters, and very short-term duration of observation.

In a large multisite trial (139), 218 patients were randomly assigned to 10 weeks of ERP guided by a therapist (n=69), ERP guided by a computer and workbook (n=74), or systematic relaxation guided by an audiotape and manual (n=75). ERP guided by a therapist consisted of 11 weekly 1-hour sessions in which therapists told patients how to conduct exposures at home but did not supervise in-session exposures. ERP guided by computer used BT STEPS, a nine-step computer-driven interactive voice response system that allows patients to telephone from home at any time of day or night and progress through a self-paced workbook that allows the patient to design and implement an individualized plan of behavior therapy. Relaxation therapy consisted of an audiotape and manual that directed the patient to practice PMR 1 hour daily. Of those who entered, 55 (80%) completed ERP, 55 (74%) completed BT STEPS, and 66 (88%) completed PMR. In ITT analyses, ERP was superior to BT STEPS, and both were superior to PMR (Y-BOCS reduction: 32% for ERP; 23% for BT STEPS; 7% for PMR). Significantly more patients receiving ERP were CGI-I:1,2 responders (60%), compared with patients receiving either BT STEPS (38%) or PMR (14%). Patients who adhered to ERP (either guided by clinician or computer) had a larger mean decrease in their symptoms than the overall mean decrease for that condition. Patients were followed for an additional 14 weeks. However, the groups received different follow-up treatment, so overall group comparisons were confounded. Of note, nonresponders to BT STEPS who were switched to clinician-guided ERP had a significant decrease in OCD severity, whereas nonresponders to ERP who were switched to BT STEPS did not. The authors concluded that minimal ERP (i.e., 11 weekly 1-hour sessions in which a therapist provides instructions only) is superior to BT STEPS and that PMR is ineffective for OCD. However, the reduction in OCD symptoms was substantially less than that seen in other studies in which therapists supervised in-session exposures (e.g., compare ITT results in Lindsay et al. [535] and Foa et al. [123]).

In a Brazilian controlled trial of group ERP (134), OCD patients were randomly assigned to 12 weeks of either group ERP (n=23) or wait-list control (n=24). Although 45% of patients were taking medications at the time of therapy, they had been taking the medication at a stable dose for at least 3 months. The group ERP was conducted in weekly 2-hour sessions in groups of seven or eight; it included in-session exposure, ritual prevention, and cognitive restructuring. In ITT analyses, group ERP was significantly superior to the wait-list condition (Y-BOCS reduction: group ERP 43%; wait-list 6%); 70% of group ERP patients were YBOCS-35% responders. Twenty-two ERP patients reevaluated after 3 months had maintained their gains. However, whether patients received additional treatment during follow-up was not stated.

A multisite trial (123) compared the efficacy of 12 weeks of ERP, clomipramine, their combination, and pill placebo in adults with OCD and without co-occurring depression. Of 122 entering randomly assigned treatment, 87 (71%) completed the study. ERP was delivered intensively for the first 4 weeks (i.e., five 2-hour sessions per week); it consisted of exposure (imaginal and in vivo), ritual prevention, and relapse prevention. During exposures, feared consequences and dysfunctional beliefs were discussed. For the remaining 8 weeks, patients received 45-minute maintenance sessions in which no in-session exposures were conducted. Patients randomly assigned to receive clomipramine or placebo were seen for 30 minutes weekly by a research psychiatrist. They received clomipramine titrated up to 200 mg/day or placebo in the first 5 weeks, with an optional increase to 250 mg/day if needed. In ITT and completer analyses, all active treatments were superior to placebo. ITT and completer response rates (CGI-I:1,2) were, respectively, 62% and 86% for intensive ERP, 42% and 48% for clomipramine, 70% and 79% for combination treatment, and 8% and 10% for placebo. Post hoc analyses (126) demonstrated that intensive ERP with or without clomipramine produced a significantly higher proportion of patients (>50%) with minimal symptoms (i.e., Y-BOCS ≤12) than either placebo (0%) or clomipramine alone (25%). However, high study refusal rates (71% of those meeting entry criteria refused to participate) and dropout rates (18% at randomization and an additional 23% before completion) may limit the widespread applicability of this study's findings.

In a Japanese study (536), 31 OCD outpatients were randomly assigned to 12 weeks of single-blind ERP plus pill placebo; fluvoxamine 150–200 mg/day (dose reached no later than week 5) plus autogenic training (psychotherapy placebo); or autogenic training and placebo. Among the 28 patients (90%) who completed treatment, ERP was significantly more effective than fluvoxamine in reducing Y-BOCS scores. Ten of 10 (100%) patients receiving ERP were Y-BOCS-35% and CGI:1,2 responders compared with 3 of 10 (30%) fluvoxamine patients and 0 of 8 (0%) placebo patients. The study is limited by small sample size, lack of double-blind ratings, and low doses of fluvoxamine.

In addition to these randomized controlled trials, several controlled trials compared ERP and different variants of cognitive therapy with and without SRI medication. These studies are reviewed in the section on cognitive therapy for OCD (Section V.C.2). Overall, these studies also found that ERP significantly reduced OCD symptoms, further supporting its efficacy for OCD. However, most of these studies lacked a placebo or nonactive control condition. Two used a wait-list control, with one (61) reporting that gradual self-controlled ERP was significantly superior to 8 weeks of wait-list control, and the other (133) finding that group ERP was superior to wait-list control.

Open trials of ERP (totaling hundreds of patients) also support the efficacy of ERP for OCD (e.g., see references 229, 537–539).

b. Factors That Affect Outcome From ERP

Several factors appear to affect the outcome of ERP. These include patient adherence to the ERP procedures (540, 541), the patient's degree of insight into the irrationality of his or her fears (with poor insight leading to worse outcome in some [208, 542, 543], but not all [209], studies), and certain co-occurring conditions. For example, severe depression and some co-occurring anxiety disorders (e.g., posttraumatic stress disorder, generalized anxiety disorder) (233, 544, 545) may negatively impact outcome. Other predictors of treatment outcome have also been reported, but none is sufficiently accurate to apply in the individual case (532, 546). Because some data suggest that certain subtypes of OCD patients (e.g., patients with severe hoarding behavior, patients without overt compulsions) may not benefit as much from ERP, modifications of standard ERP for these subtypes are being investigated (e.g., see references 121, 150). Whether the addition of formal cognitive therapy elements can improve the outcome from ERP (either for all OCD patients or for patients with co-occurring conditions such as depression) is also under investigation (Sections II.B.1, II.B.3, II.B.4, and V.C.2).

Some data suggest that ERP is most effective when delivered intensively (e.g., five sessions per week [547, 548]). On the other hand, one study found that twice-weekly ERP was comparable to intensive treatment (141), and good results have been achieved with weekly, 1-hour sessions (63). To date, no study has compared once- or twice-weekly treatment with intensive treatment in a randomized controlled design.

Whether the effects of ERP achieved in randomized controlled trials can be reproduced in routine clinical practice remains unclear. However, several large case series found that ERP (even when delivered weekly) can produce robust effects in fee-for-service settings, as long as the therapists are skilled (or supervised by those skilled) in ERP for OCD (537, 539).

c. Long-Term Outcome From ERP

Studies examining the long-term outcome of adult OCD patients after ERP have generally concluded that most patients remain treatment responders at follow-up (67, 132–134, 165, 202, 549–552). However, these findings are inconclusive for reasons that include design limitations in some studies (e.g., uncontrolled studies and/or naturalistic follow-up), methodological limitations in others (e.g., lack of standardized assessment instruments and/or blind ratings), and/or inconsistencies in whether additional treatment was received during follow-up. Recently, Simpson et al. (67) examined the posttreatment effects of intensive ERP with relapse prevention after sustained treatment discontinuation, using evaluators blind to original treatment assignment. Twelve weeks after treatment discontinuation, the relapse rate was significantly lower, and the time to relapse was significantly longer, for ERP responders (with or without concomitant clomipramine; $n=33$; 12% relapse rate) than for responders to clomipramine alone ($n=11$; 45% relapse rate). Limitations include the small sample size and short period of observation after treatment discontinuation.

Incorporating relapse prevention procedures into exposure therapy appears to improve the long-term outcome of ERP. A small randomized trial (124) examined whether ERP with ($n=10$) or without ($n=10$) relapse prevention produced different outcomes. Both groups received 3 weeks of intensive ERP (i.e., 15 daily sessions with 45 minutes devoted to imaginal exposure and 45 minutes to in vivo exposure sessions) followed by four 90-minute sessions of either relapse prevention (i.e., discussion of stressors likely to trigger OCD, meeting with a significant other to discuss maintenance of gains, and cognitive restructuring) or associative therapy (i.e., free association about OCD symptoms) combined with progressive muscle relaxation (AT-PMR). Those subjects receiving relapse prevention also received nine 15-minute phone calls over 12 weeks of follow-up. Outcome was evaluated after intensive ERP with relapse prevention and after 6 months of follow-up. Both groups had dramatic decreases in OCD symptoms after intensive ERP, without a significant difference (Y-BOCS decreases in subjects who completed the study: 66% for relapse prevention; 60% for AT-PMR). However, at 6-month follow-up the relapse prevention group showed significantly lower relapse rates than the AT-PMR group on most measures and a trend in this direction on the Y-BOCS. The authors concluded that relapse prevention helps patients maintain gains from ERP. Relapse prevention techniques are part of some standard ERP protocols (142).

d. Cognitive-Behavioral Therapy as an Augmentor of SRI Response

Data from open trials (i.e., Simpson et al. [161] [*n*=6], Tolin et al. [162] [*n*=20]) and a completed randomized trial (i.e., Tenneij et al. [163] [*n*=96]) indicate that CBT consisting of ERP can successfully augment a partial response to an adequate SRI trial. A small (*n*=14) open trial (553) also suggests that the addition of CBT consisting of exposure, response prevention, and cognitive therapy can help SRI nonresponders, although this trial lacked a control group continuing on medication alone. No data are available regarding the effect of adding cognitive therapy elements alone in attempts to augment medication response.

2. Cognitive Therapy

This section reviews studies that have examined the efficacy of cognitive therapy (CT) in the treatment of adults with OCD. For the purposes of this review, CT includes those variants of CBT that rely primarily on cognitive therapy techniques as described in Section V.C.1. The studies address three issues: whether CT without ERP is effective, whether CT is as effective as ERP and/or medication, and whether the addition of cognitive procedures to ERP leads to a better outcome.

a. Efficacy of Cognitive Therapy Without ERP

A small randomized trial involving patients who had previously failed to respond to CBT consisting of ERP compared the efficacy of group cognitive therapy to a wait-list control for OCD patients with contamination concerns (554). Eleven patients received 9 weeks of Danger Ideation Reduction Therapy (DIRT), which consisted of eight 1-hour group therapy sessions and included cognitive restructuring, expert testimony and corrective information, attentional focusing, DIRT proscribed exposure, response prevention, and behavioral experiments. Although DIRT led to significant greater changes than the wait-list control on several self-report OCD and depression measures, the effects were small (e.g., a 20% mean reduction in OCD symptoms on the MOCI). Study limitations include the small sample size, self-report measures, and use of a wait-list control.

An open trial enrolling 15 patients (555) found that individual CT in the absence of prolonged exposure led to significant improvement on several self-report OCD and depression measures (including the Y-BOCS, Obsessional Beliefs Questionnaire, and BDI). CT consisted of 14 weekly 60-minute sessions and included psychoeducation, CT procedures following Beck's method, and relapse prevention. Behavioral experiments were used to test and correct a patient's belief but did not involve prolonged exposure.

In sum, there is limited evidence to support the efficacy of pure CT (i.e., cognitive restructuring without exposure or "behavioral experiments") in the treatment of OCD.

b. Efficacy of Cognitive Therapy Versus ERP

Most direct comparisons of CT and ERP have found that these treatments produce similar results. However, strong conclusions are difficult to reach for a number of reasons. First, some variants of ERP include informal cognitive techniques (e.g., relapse prevention, cognitive restructuring during exposures) and some forms of cognitive therapy include informal exposures (i.e., behavioral experiments [behaviors that test the validity of the patient's obsessional beliefs, e.g., "If I think about a disease, my daughter will get it."]), blurring the distinction between these treatments. Second, the published studies have differed in their designs and treatment procedures (e.g., duration and frequency of treatment sessions). Third, only some studies formally monitored therapist adherence to the treatment protocols. Fourth, some studies had limited power to detect differences. Fifth, no study included a placebo group other than a wait-list control. Therefore, the treatment recommendations gleaned from these studies are necessarily specific to the procedures used and limited by these methodological weaknesses. Together, the data suggest that CT that includes behavioral experiments has similar efficacy to ERP based solely on habituation (i.e., without discussion of feared consequences or dysfunctional beliefs).

Two early studies (556, 557) examined the efficacy of rational-emotive therapy (RET) based on the work of Ellis (558); this CT program included the identification and challenge of irrational beliefs but no behavioral experiments. Both studies found that therapist-administered RET helped OCD patients and was similar in efficacy to self-controlled ERP. One study (557) concluded that RET followed by self-controlled ERP was no better than self-controlled ERP alone. However, both studies had small samples (i.e., $n \leq 11$ per condition) and used a less than optimal ERP format (e.g., self-controlled as opposed to therapist-guided exposure). Another small open trial in six subjects compared RET with ERP and thought stopping and found that RET was more effective than ERP for purely obsessional patients who had no covert rituals, and that thought stopping was not helpful at all (151).

A larger randomized study by van Oppen et al. (559) compared outcomes in 28 patients who received 16 weeks of CT based on the model of Beck (530) and Salkovskis (531), and 29 patients who received self-controlled ERP. This CT program targeted dysfunctional beliefs considered to be central to OCD (i.e., the overestimation of danger and inflated personal responsibility), and specifically included behavioral experiments. For both conditions,

therapy was delivered weekly in 45-minute sessions. Among the subjects who completed the trial, both treatments led to significant and clinically meaningful improvement in OCD. Although there were no significant group differences, CT appeared somewhat superior (Y-BOCS reduction: 45% for CT; 32% for ERP). However, a less than optimal ERP format (i.e., self-controlled exposure) was utilized, and the CT program used behavioral experiments. Half the patients in this study participated in a multicenter trial comparing fluvoxamine, ERP, and CT, described below.

Van Balkom et al. (61) randomly assigned 117 patients to one of five conditions: fluvoxamine plus ERP, ERP, CT, fluvoxamine plus CT, or wait-list control. At baseline, patients on average had mild depressive symptoms. Full results are presented for the 70 patients who completed 16 weeks of active treatment and the 16 patients who completed the 8-week wait-list condition. The mean dose at week 16 in both fluvoxamine conditions was 197 (±82) mg/day. All therapy sessions were 45 minutes long. CT and ERP were delivered as in the van Oppen study (559) described above. CT targeted dysfunctional OCD beliefs and included behavioral experiments. ERP consisted of gradual self-controlled exposure in vivo with gradual self-imposed response prevention. At week 16, all active treatments led to a significant decrease on all OCD measures, with no significant differences between the treatment groups (Y-BOCS reduction for subjects who completed the trial: 46% for CT [n=19]; 32% for ERP [n=19]; 43% for fluvoxamine plus CT [n=14]; 49% for fluvoxamine plus ERP [n=18]). The authors concluded there was no reason to combine SRIs and CBT (either CT or ERP) in OCD adults without severe co-occurring mood disorder. However, neither the ERP nor the fluvoxamine treatments were optimized. Moreover, the combination groups received only 10 therapy sessions that started after 8 weeks of fluvoxamine treatment, whereas the groups receiving ERP or CT alone received 16 therapy sessions. Some of these patients were followed naturalistically for 6 months, but the fact that they received varied treatment during this follow-up period precludes strong conclusions (549).

A French multisite randomized trial (62) compared the outcome of patients who received 20 hours of either CT (n=32) or ERP (n=33) over 16 weeks. CT treatment consisted of twenty 1-hour individual sessions following the Beck and Salkovskis model (i.e., challenging of dysfunctional beliefs); behavioral experiments to "confront feared situations to modify thoughts" were also used. ERP consisting of therapist-aided exposure with response prevention was delivered in an intensive phase (4 weeks of two 2-hour individual sessions per week) and a maintenance phase (12 weeks of one 40-minute booster session every 2 weeks). In those patients who completed treatment, both treatments led to significant and substantial reductions in OCD symptoms (Y-BOCS reduction: 44% for CT; 42% for ERP), and many patients were YBOCS-25% responders (77% for CT; 70% for ERP). There were no significant group differences. Patients were followed after treatment to week 52, but 26% of the patients were lost to follow-up, and whether those followed received additional treatment is unclear.

In a Canadian randomized trial (133), OCD patients (48% who were taking a stable dose of medication and 50% of whom had a co-occurring Axis I disorder) were randomly assigned to 12 weeks of CT (n=18), ERP (n=16), or wait-list control (n=33). Patients in the wait-list condition were randomly assigned to receive CT or ERP after the 12-week delay, and their data were pooled with the data from those who received active treatment initially. Treatment was delivered in groups and consisted of 2.5-hour sessions delivered once per week. Based on the work of Salkovskis (560), Freeston et al. (64), and van Oppen and Arntz (561), the CT focused on challenging appraisals of intrusive thoughts; behavioral experiments were used to collect evidence for and against alternative appraisals. ERP consisted of in-session and between-session exposure and ritual prevention focused on producing habituation, and relapse prevention; discussion of cognitive beliefs was proscribed. In those patients who completed treatment, both treatments were superior to wait-list control; however, group ERP was superior to group CT in the pooled sample (Y-BOCS decrease: 26% for CT; 39% for ERP). Of the 63 patients who completed treatment, 16% of CT patients and 38% of ERP patients recovered (defined as a Y-BOCS score decrease ≥6 points and a total score <12). Of note, 12 of 49 CT and 2 of 44 ERP patients dropped out of the study after learning of their randomization and before starting treatment. Moreover, nearly twice as many patients taking medication received ERP than received CT. At 3-month follow-up, there was still a significant advantage for ERP over CT. However, these data are limited by the fact that patients were not prohibited from obtaining treatment during follow-up.

In another Canadian controlled trial (63), patients were randomly assigned to receive individual CT (n=37) or ERP (n=34). Both treatments consisted of 12 weekly 60-minute sessions and followed the same format as in the study of McLean et al. (133) described above. Specifically, the CT focused on challenging dysfunctional beliefs but included behavioral experiments; the ERP included relapse prevention but no cognitive restructuring. In those who completed treatment (n=59, 83%), OCD severity improved significantly in both treatment groups, with no significant group differences (Y-BOCS score reduction:

56% for CT; 52% for ERP). Of those patients who completed the study, 67% of CT and 59% of ERP patients recovered (defined as a Y-BOCS score decrease ≥6 points and a total score <12). Both groups also had a significant decrease in depressive symptoms and in dysfunctional beliefs. The authors concluded that individual ERP utilizing only habituation was similar in efficacy to individual CT that included behavioral experiments, and that both treatments reduce OCD symptoms. Additional CT techniques without exposure are described in case reports (129, 130).

c. Adding Cognitive Therapy to ERP

Some data suggest that ERP is more effective if it includes not only habituation but also discussion of feared consequences and dysfunctional beliefs (120, 121). One small study suggests that the addition of relapse prevention helps patients maintain their gains (124). Whether CT added to ERP helps OCD patients with co-occurring conditions (e.g., depression) is under investigation.

An early study (562) found that both ERP and ERP plus "self-instructional" talk (i.e., emitting more positive statements after imagining being exposed to some feared stimulus) led to clinically significant improvement. However, the small sample (n=8 vs. n=7) and the uncertain diagnostic validity of the sample (given the lack of standard criteria at that time) preclude strong conclusions.

A Norwegian randomized trial (122) examined whether the ERP protocol of Kozak and Foa (142), which includes discussion of feared consequences and dysfunctional beliefs during exposures, could be improved by the addition of formal CT elements based on Beck's work (530). Patients were randomly assigned to receive ERP plus CT, ERP plus relaxation training, or wait-list control for 6 weeks. After 6 weeks, those assigned to the wait-list control were randomly assigned to receive one of the active treatments. The final sample consisted of 16 patients who received ERP plus CT and 19 patients who received ERP plus relaxation training; 34% were taking a stable dose of medication during the trial. Therapy consisted of 2-hour sessions twice weekly, for a total of 12 sessions. Each session consisted of 1.5 hours of ERP and 30 minutes of either CT (based on the Beck model and focused on either co-occurring conditions or faulty OCD beliefs) or relaxation training (progressive muscle relaxation). ITT analysis indicated that both active groups did significantly better than wait-list controls, with no differences between the two active conditions (Y-BOCS reduction: 33% for ERP plus CT; 28% for ERP plus relaxation training). However, more patients completed ERP plus CT (15/16) than ERP plus relaxation (12/19). The authors concluded that the addition of CT to ERP (delivered as outlined in Kozak and Foa [142]) may reduce the dropout rate but does not necessarily enhance efficacy. However, the sample was relatively small, and there were other methodological limitations (e.g., wait-list design, many ratings done by the therapist, more exposure time for patients who received ERP plus relaxation training).

Recent studies have also examined whether CT added to ERP can improve outcome (120, 122).

3. Group and Multifamily Behavioral Treatment

A limited number of studies have investigated group and multifamily behavioral treatments for OCD.

A 12-week unblinded random-allocation study (132) compared group (n=30) and individual ERP (n=31) with an active control (progressive muscle relaxation; n=32). Patients with major depression or Axis II disorders were excluded. Both active treatments were superior to the control treatment, as reflected in changes in Y-BOCS, BDI, and Social Adjustment Scale scores. However, response to treatment was faster with individual behavior therapy. The authors concluded that group therapy ERP was useful for less severe OCD. From an efficiency standpoint, the individual treatment consumed 720 staff hours compared with 48 hours in the group therapy condition.

A randomized trial (133) (consisting of 12 weeks of weekly 2.5-hour groups) compared group CT with behavioral experiments (n=33) and group ERP (n=40) against a wait-list control. The control subjects were later randomly assigned to either active treatment. Subjects were diagnosed with DSM-IV OCD of greater than 1 year's duration and had been taking medication on a stable regimen for ≥3 months. Ninety-three subjects entered the trial, 76 (82%) began treatment, and 63 (68%) completed treatment. Both active treatments were significantly superior to the control condition as reflected in change in Y-BOCS scores. The effect sizes (Cohen's d) were 1.62 for ERP (n=16), and 0.98 for CT (n=18). For those completing treatment, the difference in the proportions of "recovered" subjects (defined as Y-BOCS score decrease ≥6 points *and* final score <12) was not significant: ERP (38%, n=32) and CBT (16%, n=31). At 3-month follow-up, ERP was associated with a significantly greater recovery rate among subjects who completed the treatment: ERP (45%) and CBT (13%). The ERP group included more subjects using medication, but in the analyses this did not affect improvement. This study suggested that group ERP was marginally superior to group CT. Caution in interpreting these results is warranted, because more subjects in the ERP group were taking medication, and because CT was characterized by a higher refusal rate among subjects accepted for treatment.

A single-blind, randomized trial compared 12 weeks of weekly 2-hour group therapy sessions combining ERP with cognitive therapy and homework assignments (group

CBT) (n=23) against a wait-list control (n=24) (134). The group CBT included exposure, ritual prevention, and cognitive restructuring. Seventy percent of those in group CBT were YBOCS-35% responders compared with 4% of controls. The Y-BOCS score effect sizes (*not* Cohen's d) in the ITT groups were 1.33 for the group CBT group and 0.43 for the controls. The therapeutic gains were maintained at 3-month follow-up. Group CBT was associated with a significant improvement in the quality of life as measured by the Abbreviated WHOQOL. Nearly half the subjects were maintained on stable medication regimens, but this did not appear to influence the effect of active treatment. These and other reports suggest the utility of group behavioral therapies in the treatment of OCD; however, additional study is warranted.

An uncontrolled, double-blind study without random assignment compared group CBT (including ERP) (n=17) and multifamily CBT (n=19) (136). In each treatment there were ten to twelve 2-hour sessions monthly. This small study found that both modalities were effective, with a significant decrement in the Y-BOCS score in both components, and a significant decrease in the Sheehan Disability Inventory in the group CBT component. This study provides support for both group approaches. There are too few studies of multifamily CBT to provide sufficient evidence to recommend its use.

In an unblended, random allocation study in India, patients who had had no prior CBT but who had failed pharmacological treatment were assigned to either a treatment in which family members functioned as co-therapists conducting desensitization and ERP (n=15) or the same treatment without a family member co-therapist (n=15) (135). The treatment group with a family member co-therapist showed significantly greater improvement at 12 weeks and at 1-month follow-up on the MOCI and the Global Assessment of Severity scale. This small study suggests the utility of family co-therapists, but the results may not be generalizable to other cultures and are limited by the absence of a control group and the variability to be expected among families.

4. Kundalini Yoga

In a 12-week study (563), subjects with a primary DSM-III-R diagnosis of OCD, a minimum Y-BOCS score of 15, and no medical contraindications to yoga were randomly assigned to 12 weekly 2-hour group sessions of Kundalini yoga (n= 12) or 1-hour group sessions of mental mindfulness and relaxation response management (n=10). Both groups were instructed to practice at home daily. Seven subjects completed each treatment arm. The subjects in the yoga group who completed the trial experienced a mean Y-BOCS score decrease of 38% (9.4 points), compared with a 14% decrease (2.9 points) for the control group. In the ITT analyses, the yoga group's mean decrease in Y-BOCS score was significant (5.5 points), but the mean decrease for the control group (2.0 points) was not. In both groups, an unspecified but equal number of subjects had been taking stable doses of anti-OCD medications for at least 3 months before randomization. Yoga was apparently well tolerated, but the reasons for dropout are not given. This small study requires replication by an independent group before any conclusion about the effectiveness of yoga can be drawn.

D. COMBINED THERAPY

Only six randomized trials have directly addressed whether the combination of an SRI and CBT consisting of ERP is superior to either treatment alone in adults with OCD, and limitations in their designs and/or procedures prevent definitive conclusions. Some studies also compared SRI monotherapy with ERP monotherapy. Few studies had adequate sample sizes to detect small differences between treatments, even if such differences did exist. Moreover, some studies excluded patients with significant comorbidity even though comorbidity is common in OCD and such patients may be those who would benefit most from combination treatment. Finally, certain design decisions (e.g., how the treatments were delivered) may have prevented the detection of important differences between combination treatment and monotherapy.

Despite these problems, the available data support the idea that combination therapy can be superior to monotherapy in some OCD patients but that it is not necessary for all OCD patients (166, 167). In particular, one study found that combination therapy is superior to ERP monotherapy in OCD patients with co-occurring depression (164). In OCD patients without co-occurring depression, another study found that combination therapy and intensive ERP therapy alone were each superior to SRI monotherapy (123).

Marks et al. (564) compared the outcome of 40 OCD patients randomly assigned to receive oral clomipramine or pill placebo plus 30 sessions of CBT consisting of ERP. The study design was complex: during weeks 0–4, patients received either clomipramine or placebo; during weeks 4–10, patients also received either 30 sessions of ERP or 15 sessions of relaxation training followed by 15 sessions of ERP. A direct comparison of the effects of clomipramine plus ERP, ERP plus placebo, clomipramine plus relaxation training, and placebo plus relaxation training could only be made at week 7. At that time, patients receiving clomipramine plus ERP (n=10) had more improvement

in rituals than patients receiving ERP plus placebo (n=10) or clomipramine plus relaxation training (n=10); however, there was no significant interaction of clomipramine and ERP. The complex design, small sample, lack of standard OCD measures, and treatment procedures (e.g., the effects of clomipramine were likely underestimated at week 7) preclude strong conclusions.

A separate study (565) compared the outcome of 49 patients randomly assigned to receive one of four treatments: 6 months of clomipramine and 23 weeks of antiexposure instructions (clomipramine plus antiexposure); 6 months of clomipramine and 23 weeks of self-controlled ERP (clomipramine plus ERP [self]); 6 months of clomipramine and 8 weeks of self-controlled ERP, followed by therapist-aided ERP from weeks 8 to 23 (clomipramine plus ERP [self and therapist]); or 6 months of placebo and 8 weeks of self-controlled ERP, followed by therapist-aided ERP from weeks 8 to 23 (placebo plus ERP [self and therapist]). At week 8, clomipramine plus ERP (self, n=25) produced significantly more improvement in rituals and depression than placebo plus ERP (self, n=12). However, at week 23, clomipramine plus ERP (self and therapist, n=10) showed no superiority over placebo plus ERP (self and therapist) plus placebo (n=8). At week 8, clomipramine plus ERP (self, n=13) also produced significantly more improvement than clomipramine plus antiexposure (n=12) in rituals and depression. Only three of the subjects in the clomipramine plus antiexposure group improved enough to continue, precluding further comparisons. The authors concluded that the combination of clomipramine and ERP therapy had a small transitory additive effect compared with placebo plus ERP therapy. However, the complex design, small sample, lack of standard OCD measures, and treatment procedures (e.g., the clomipramine groups only achieved doses ranging from 127–157 mg/day) preclude strong conclusions.

Cottraux et al. (165) randomly assigned 60 adult patients with OCD to 24 weeks of fluvoxamine with ERP (fluvoxamine plus ERP), fluvoxamine with instructions not to engage in ERP (fluvoxamine plus antiexposure), or placebo plus ERP. Of the 60 patients who entered, 44 (73%) completed all 24 weeks (n=16, 13, and 15, respectively); of these 44, 19 (43%) entered with a major depressive or dysthymic disorder (mean 17-item Ham-D score= 19). ERP therapy consisted of eight weekly sessions that included imaginal ERP during sessions and self-controlled ERP, followed by 16 weeks of therapist-guided ERP. Among those patients who completed treatment, all groups improved on some measures of rituals and depression, but only the fluvoxamine plus ERP group improved on all measures at week 24. The combined fluvoxamine treatment groups had the largest percent reduction in the duration of rituals per day (fluvoxamine plus ERP=46%; fluvoxamine plus antiexposure=42%; placebo plus ERP=25%) and the largest percentage of patients who, by self-report, had more than a 30% reduction in rituals per day (fluvoxamine plus ERP=69%; fluvoxamine plus antiexposure=54%; placebo plus ERP=40%); however, these group differences were not statistically significant. Study limitations include the small sample, the lack of standard OCD measures, and the limited information about the treatment procedures (e.g., the ERP protocol consisted of weekly sessions of an unspecified duration, and other psychosocial interventions were provided "as needed").

Hohagen et al. (164) randomly assigned 60 adults with OCD to receive fluvoxamine plus CBT or placebo plus CBT. Many patients had co-occurring mood, anxiety, and personality disorders (mean 21-item Ham-D score=19), and many (92%) had received prior treatment (84% had taken medication, 35% had prior CBT). The mean dose of fluvoxamine was 288 mg/day (range=250–300 mg/day). CBT was conducted weekly for at least 3 hours and included therapist-aided exposure as well as cognitive restructuring. After 9 weeks of treatment, both groups showed significant reductions in OCD severity. However, there were significantly more YBOCS-35% responders in the fluvoxamine plus CBT group (87.5%) than in the placebo plus CBT group (60%). Post hoc analyses revealed that 1) both groups improved significantly and comparably on compulsions, but the fluvoxamine plus CBT group improved significantly more on obsessions; and 2) patients with co-occurring depression fared better if they received fluvoxamine plus CBT. The authors concluded that combination therapy should be used when obsessions dominate the clinical picture or when a secondary depression is present. Limitations include the lack of data on whether the two groups differed in their response to prior treatment, the fact that only 49 patients entered the final analysis because 9 were removed to equate baseline Y-BOCS scores in the two groups, and the fact that two patients dropped out for clinical reasons.

Van Balkom et al. (61) randomly assigned 117 patients to receive one of five conditions: fluvoxamine plus ERP, ERP, CT, fluvoxamine plus CT, or wait-list control. At baseline, patients on average had mild depressive symptoms. Full results are presented for the 70 patients who completed 16 weeks of active treatment and the 16 patients who completed the 8-week wait-list condition. The mean fluvoxamine dose at week 16 in both fluvoxamine conditions was 197 (±82) mg/day. All therapy sessions were 45 minutes long. ERP consisted of gradual self-controlled exposure in vivo with gradual self-imposed response prevention. At week 16, all active treatments led to a significant decrease on all OCD measures, with no significant differences between the treatment groups.

The authors concluded there was no reason to combine SRIs and CBT (either ERP or CT) in OCD adults without severe co-occurring mood disorder. However, neither the ERP nor the fluvoxamine dosing was optimized. Moreover, the combination group received only 10 ERP sessions, whereas the group receiving ERP alone received 16 sessions.

Foa et al. (123) compared treatment outcome in 122 adult OCD patients randomly assigned to receive intensive ERP, clomipramine, clomipramine plus intensive ERP, or placebo. Patients with major depressive disorder (and a Ham-D ≥ 18) were excluded. Mean daily doses of clomipramine during the last study week for all who entered and all who completed the trial, respectively, were 196 and 235 mg/day for clomipramine patients and 163 and 194 mg/day for clomipramine plus intensive ERP patients. ERP was delivered intensively for the first 4 weeks (i.e., two information-gathering sessions, fifteen 2-hour sessions conducted over 3 weeks, two home visits); this intensive phase was followed by eight 45-minute weekly maintenance sessions over the next 8 weeks. Patients receiving clomipramine plus intensive ERP began both treatments simultaneously. At week 12, all active treatments were superior to placebo at reducing OCD symptoms. In addition, clomipramine plus intensive ERP and ERP did not significantly differ from each other, but each was superior to clomipramine alone. For all who entered treatment and all who completed the 12-week trial, the CGI-I:1,2 response rates were, respectively, 70% and 79% for clomipramine plus intensive ERP, 42% and 48% for clomipramine, 62% and 86% for ERP, and 8% and 10% for placebo. The authors concluded that clomipramine, intensive ERP, and their combination are all efficacious treatments for OCD. In addition, in OCD patients without co-occurring depression, intensive ERP was superior to clomipramine. The authors noted several factors that may have limited their ability to detect a superiority of combination treatment over intensive ERP monotherapy (e.g., the exclusion of patients with co-occurring depression, the potency of intensive ERP, the fact that the combination group did not achieve maximum clomipramine doses). Study limitations include the lack of data on patients who dropped out after randomization but before treatment started and the lack of systematic data on subjects' prior treatment history. Interpretation of these results (123, 126) is also limited by uncertainty as to whether the treatment groups were equally treatment resistant at baseline and by high study refusal rates and dropout rates.

In the absence of definitive data, combination treatment (SRI medication plus CBT consisting of ERP) is appropriate in clinical situations in which there are co-occurring disorders that are SRI responsive or there has been a partial response to monotherapy (163), and in efforts to reduce the chance of relapse when medication is discontinued (67).

E. DISCONTINUATION OF ACTIVE TREATMENT

Four double-blind SRI discontinuation studies in adults with OCD have been published. Each concerned a different SRI and used a different design (e.g., length of observation and method of placebo substitution) and a different relapse definition. Each produced different results.

Pato et al. (199) found that 89% of the 18 patients who had responded to clomipramine had "substantial recurrence" (not further defined) of OCD 7 weeks after they were blindly switched (over 4 days) to placebo. Romano et al. (201) found no significant differences in 1-year estimates of relapse rates among patients who had responded after 5 months of fluoxetine treatment between 36 patients who continued to take fluoxetine (21%) and 35 patients who were switched to placebo (32%); relapse was defined as a ≥50% loss of improvement on the Y-BOCS, a Y-BOCS score of ≥19, and a CGI-I rating of much or very much worse relative to the end of treatment. Koran et al. (200) found that it was uncommon for patients who responded to sertraline to discontinue the medication because of relapse or insufficient response over 28 weeks, regardless of whether they continued to take sertraline (3% [3/108]) or were switched over 2 weeks to placebo (4% [5/113]); relapse was defined as a Y-BOCS increase of ≥5 points, a total Y-BOCS score of ≥20, and a ≥1-point increase in CGI-I score relative to the end of acute treatment at three consecutive visits at 2-week intervals. Rates of relapse or discontinuation because of insufficient response were 9% for sertraline and 24% for placebo, a significant difference. Finally, Hollander et al. (80) found that patients who had responded to 9 months of paroxetine treatment who continued to take paroxetine for 6 months had a significantly lower relapse rate (37.7%) than those switched immediately to placebo (58.8%) and a longer time to relapse (62.9 days vs. 28.5 days); relapse was defined as a return to the pretreatment Y-BOCS score or a ≥1-point increase on the CGI-severity (CGI-S) scale (566) relative to the end of treatment. In summary, using different SRIs, different study designs, and different relapse criteria, double-blind discontinuation studies reported SRI relapse rates ranging from a low of 4% over 28 weeks (200) to a high of 89% over 7 weeks (199).

An unblinded study of 130 OCD patients (177), in which drug discontinuation was instituted after response to 6 months of open treatment, reported significantly higher 6-month relapse rates for the patients whose medication was discontinued: 8% (clomipramine 150 mg/day) ver-

sus 46% (no drug), 0% (fluoxetine 40 mg/day) versus 40% (no drug), and 8% (fluvoxamine 300 mg/day) versus 62% (no drug) (177). Equally large or larger disparities were present after 1 and 2 years of treatment versus no treatment, and relapse rates were higher. Relapse was defined as a Y-BOCS increase of ≥25% *plus* a CGI-I score indicating much or very much worse relative to the end of treatment. These data suggest both that SRIs may not fundamentally differ in the long-term durability of treatment response after treatment discontinuation and that most patients will eventually relapse after stopping SRI treatment.

In a review of 16 CBT studies that used ERP, Foa and Kozak (202) concluded that patients receiving ERP (with and without concomitant medication) did well long-term. Of 376 treated patients, 76% were responders at follow-up (mean=29 months; range=6–72 months). Of responders to acute ERP treatment (with or without medication), the proportion losing their response during follow-up was 20% or less in most studies. While suggestive, these findings are inconclusive because of 1) design limitations in some studies (e.g., uncontrolled studies with naturalistic follow-up); 2) methodological limitations in others (e.g., lack of evaluators blind to original treatment assignment); 3) differences in determining "response"; 4) inconsistencies in whether treatment during follow-up was permitted (and reported); and 5) differences in length of follow-up. Further complicating any comparison with SRI relapse rates is the fact that the relapse definition employed in this review (i.e., loss of response) differs from that used in the SRI studies.

A multi-site study that compared the effects of clomipramine and intensive ERP after 12 weeks of treatment (123) and again 12 weeks after treatment discontinuation (67) found that subjects who responded to intensive ERP (with or without concomitant clomipramine) had a significantly lower relapse rate (12%) and longer time to relapse after treatment discontinuation than did subjects who responded to clomipramine alone (45%); relapse was defined as a return to baseline severity on the CGI-S scale. Post hoc analyses of these data generally supported these findings, since most of the relapse criteria examined produced the same outcome—albeit with substantial variability—depending on the specific criteria used for relapse (203). However, high study refusal rates (71% of those meeting entry criteria refused to participate) and dropout rates (18% at randomization and an additional 23% before completion) may limit the widespread applicability of this study's findings.

Together, these data suggest that ERP treatment response may be more durable, at least in the short run, than response to some SRIs after they are discontinued. However, the observed differences could be explained by other factors, including clinical characteristics of the subjects studied, differences in the length of follow-up, the intensity of treatment prior to treatment discontinuation, the rate of medication taper, and the relapse criteria. Because of these differences, no definitive conclusions about the relative durability of SRI and ERP treatment effects can be drawn from these studies.

Part C
FUTURE RESEARCH NEEDS

Although current therapeutic approaches can alleviate symptoms of OCD, additional research is needed to enhance existing treatments and develop additional therapeutic options. More specifically, studies are needed to determine whether modifications in treatment regimens can improve the proportion of responders and the degree, rapidity, and permanence of response. For example, studies could show whether higher doses or more rapid titration of SRIs results in faster treatment response and greater symptom relief. A number of medications (e.g., mirtazapine, pindolol, stimulants, opiate-receptor agonists, glutamate-modulating agents, inositol, ondansetron, some anticonvulsants, lithium) have shown some efficacy in preliminary research either alone or as augmentation strategies; however, these agents and related approaches require further study in larger randomized trials. The use of adjunctive antipsychotic medications and other promising somatic treatments (i.e., transcranial magnetic stimulation, deep brain stimulation) also need additional investigation. The recent introduction of a monoamine oxidase inhibitor administered by skin patch, which at initial doses does not require dietary restrictions, allows a re-investigation of the possible utility of this class of medication in treating OCD.

Further studies of psychosocial therapies are also necessary. For example, with CBT, it will be important to determine the relative efficacies of different CBT treatment elements and the optimal schedule (e.g., treatment session length and frequency, number of sessions) for administering CBT in the acute, continuation, and maintenance phases of treatment. In designing such research, the treatment schedules investigated will likely differ with the goals of treatment (e.g., induce or maintain response or remission, reduce risk of relapse). Because CBT can be administered using a variety of formats (e.g., individual, group, supplementary self-help manuals), it will be important to compare the efficacies of these approaches. Other psychosocial therapies, such as therapies that involve the family in the patient's CBT, also require further study.

In terms of approaches to combining medications and psychosocial therapies, more studies are needed to determine optimal methods to achieve the fastest onset of therapeutic action, the greatest degree of response, and the least likelihood of relapse during active treatment and following treatment discontinuation. It is also crucial to develop and test strategies for relapse prevention as well as to identify the necessary length of psychotherapy and of pharmacotherapy before treatment can be safely discontinued.

In addition to further investigating existing treatments for OCD, it is equally important to develop new therapeutic approaches to initial treatment or new augmentation strategies for patients who have an inadequate response to first-line medications. Such approaches might involve new psychosocial treatments, including psychotherapies, or new somatic treatments, including pharmacotherapies. Rehabilitation methods for those who have been disabled also require study.

Development of new therapeutic modalities would be aided by an improved understanding of the neurobiological alterations associated with OCD and with response to OCD treatments. For example, identifying susceptibility genes for OCD could provide insight into the pathogenesis of the disorder, establish a means to identifying individuals at high risk, and perhaps lead to the development of more rational and effective therapies. Advances in pharmacogenetics, including gene chip techniques, could help identify new neurochemical targets for pharmacotherapy and predict response or side effects to particular medications or to classes of medications. Other markers (e.g., blood, electroencephalogram, neurocognitive measures, neuroimaging results or other neurobiological signs) may also be useful in understanding the neurobiological bases of OCD and in identifying early effects of medications or psychotherapy that predict treatment outcomes for individual patients. For example, several small studies (567, 568) using PET show correlations between rates of glucose metabolism in specific brain regions and response of OCD symptoms to medications or behavioral therapy. Developing a valid animal model for OCD would also enhance our knowledge of the underlying pathophysiologic basis of the disorder and aid in identifying and developing new treatment options.

With all therapeutic approaches to OCD, studies of *effectiveness* will be required to supplement the findings of *efficacy* studies. In addition, studies need to provide more information that will help target specific treatment approaches to individual patients. For example, individuals with specific subtypes of OCD (e.g., hoarding, contamination, mental compulsions) or those with specific co-occurring symptoms or disorders (e.g., co-occurring tics or co-occurring schizotypal personality disorder) may exhibit better responses to specific treatments or combinations of treatments. The optimal schedule and the effective elements of treatment may also differ by OCD symptom type or co-occurring condition.

Interpretation and dissemination of future research would be aided by more consistent use of the CONSORT recommendations in designing and reporting randomized treatment trials (569, 570) and by including details on study power and effect sizes. Utilizing a reliable and valid written self-rating scale to measure OCD symptom intensity may be useful in future studies. Standardizing the definitions of degrees of treatment response, resistance, remission, and relapse following the models of the International Treatment Refractory OCD Consortium (152) and Simpson et al. (126, 203) would also be helpful.

In order to make the advances in treatments for OCD available to more individuals with the disorder, health services research on OCD and its treatment is needed. Such research might help find ways to increase the availability of effective treatments such as CBT or of OCD treatment in general (e.g., across states and payers). Given the typical delays between OCD onset and initiation of treatment, there is a need for a sensitive and specific self-rated OCD screening questionnaire for use in primary care settings. An improved understanding of the public health impact of OCD (e.g., direct and indirect costs of OCD via health care, premature death, co-occurring illnesses, lost productivity of OCD patients, and lost work time of relatives caring for an OCD patient) is also important and could lead to specific approaches to reducing disability and improving patients' quality of life.

APPENDIX: EDUCATIONAL RESOURCES FOR PATIENTS AND FAMILIES

The American Psychiatric Association does not vouch for or endorse the accuracy of the information contained in any of the publications or Web sites listed in this appendix at the time of writing or in the future, although they are believed to be generally trustworthy at the time of writing. The clinician should review a book or visit a Web site before recommending it to a patient.

RESOURCES FOR OCD

1. Baer L: Getting Control: Overcoming Your Obsessions and Compulsions. New York, Plume Books, 2000.
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22. van Noppen B, Pato M, Rasmussen S: Learning to Live With OCD. New Haven, CT, Obsessive Compulsive Foundation, 2003.
23. Waltz M: Obsessive-Compulsive Disorder: Help for Children and Adolescents. Sebastopol, CA, O'Reilly Press, 2000.

Obsessive Compulsive Foundation

676 State St.
New Haven, CT 06511
Tel: 203-401-2070
www.ocfoundation.org

Obsessive-Compulsive Information Center

Information Centers
Madison Institute of Medicine
7617 Mineral Point Rd.
Suite 300
Madison, WI 53717
Tel: 608-827-2470
www.miminc.org/aboutocic.html

Scrupulous Anonymous

Offers a monthly newsletter for those with the religious/moral questioning form of OCD.

http://mission.liguori.org/newsletters/scrupanon.htm

San Francisco Bay Area Resource & Internet Guide for Extreme Hoarding Behavior, Clutterers Syndrome, or Pack Rat Syndrome
www.hoarders.org

American Academy of Child and Adolescent Psychiatry
Provides "fact sheets" for families about OCD, Tourette's disorder, anxiety disorders, and other disorders, as well as information about locating treating clinicians.

3615 Wisconsin Ave., NW
Washington, DC 20016-3007
Tel: 202-966-7300
Facts for Families database:
www.aacap.org/page.ww?section=Facts+for+Families&name=Facts+for+Families

RESOURCE FOR TIC DISORDERS

Tourette Syndrome Association, Inc.
42-40 Bell Blvd.
Bayside, NY 11361
Tel: 718-224-2999
www.tsa-usa.org

RESOURCES FOR PANIC DISORDER AND SOCIAL ANXIETY DISORDER

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Anxiety Disorders Association of America
8730 Georgia Ave.
Suite 600
Silver Spring, MD 20910
Tel: 240-485-1001
www.adaa.org

Anxiety Treatment and Research Centre
6th Floor, Fontbonne Building
St. Joseph's Healthcare, Hamilton
50 Charlton Ave., East
Hamilton, ON L8N 4A6
Canada
Tel: 905-522-1155
www.anxietytreatment.ca

SocialAnxietySupport.com
www.socialanxietysupport.com

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U.S. Department of Veterans Affairs, National Center for Posttraumatic Stress Disorder

www.ncptsd.va.gov

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Autism Society of America

7910 Woodmont Ave.
Suite 300
Bethesda, MD 20814-3067
Tel: 1-800-3AUTISM
301-657-0881
www.autism-society.org

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Debtors Anonymous

General Service Office
P.O. Box 920888
Needham, MA 02492-0009
Tel: 781-453-2743
www.debtorsanonymous.org

RESOURCES FOR KLEPTOMANIA

Cleptomaniacs & Shoplifters Anonymous (CASA)

Terry S. / C.A.S.A.
P.O. Box 250008
Franklin, MI 48205
Tel: 248-358-8508
www.shopliftersanonymous.com

National Association for Shoplifting Prevention

380 N. Broadway
Suite 306
Jericho, NY 11753
Tel: 1-800-848-9595
www.shopliftingprevention.org

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2. Grant JE, Kim SW: Stop Me Because I Can't Stop Myself: Taking Control of Impulsive Behavior. New York, McGraw-Hill, 2003.
3. National Council on Problem Gambling and National Endowment for Financial Education: Personal Financial Strategies for the Loved Ones of Problem Gamblers. Greenwood Village, CO, National Endowment for Financial Educations, 2000.

Gamblers Anonymous

Provides limited information on problematic gambling and access to local meetings, which are modeled on the 12-step methods of Alcoholics Anonymous.

P.O. Box 17173
Los Angeles, CA 90017
Tel: 213-386-8789
www.gamblersanonymous.org

Council on Compulsive Gambling of New Jersey

Provides articles for the public, a directory of other state Councils on Compulsive Gambling, and links to related sites.

3635 Quakerbridge Rd.
Suite 7
Hamilton, NJ 08619
Tel: 1-800-GAMBLER
609-588-5515
www.800gambler.org

RESOURCES FOR NONPARAPHILIC SEXUAL DISORDERS

Sexaholics Anonymous

Provides publications and access to meetings across the United States, which are modeled on the 12-step program of Alcoholics Anonymous.

P.O. Box 3565
Brentwood, TN 37024
Tel: 1-866-424-8777
615-370-6062
www.sa.org

Sexual Addicts Anonymous

Provides access to publications and local chapter meetings.

P.O. Box 70949
Houston, TX 77270
Tel: 1-800-477-8191
713-869-4902
www.sexaa.org

Sexual Compulsives Anonymous (SCA)

Provides a list of meetings and a pen pal program controlled by SCA.

P.O. Box 1585
Old Chelsea Station
New York, NY 10011
Tel: 1-800-977-HEAL
212-606-3778
www.sca-recovery.org

Society for the Advancement of Sexual Health

Provides information about sexual compulsions, addresses of 12-step programs, and recommended readings.

P.O. Box 725544
Atlanta, GA 31139
Tel: 770-541-9912
www.ncsac.org/general/index.aspx

RESOURCES FOR TRICHOTILLOMANIA

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Trichotillomania Learning Center
207 McPherson St.
Suite H
Santa Cruz, CA 95060-5863
Tel: 831-457-1004
www.trich.org

INFORMATION ON THE USE OF MEDICATION DURING PREGNANCY AND BREASTFEEDING

California Teratogen Information Service and Clinical Research
Tel: 1-800-532-3749 (CA only)
610-543-2131
www.otispregnancy.org/ctis.html

Massachusetts General Hospital Women's Mental Health Program
www.womensmentalhealth.com

Motherisk.com
Database maintained by the Toronto Hospital for Sick Children

www.motherisk.com

RESOURCES FOR GENERAL INFORMATION ON MENTAL DISORDERS AND MEDICATIONS

National Institute of Mental Health (NIMH)
Public Information and Communications Branch
6001 Executive Blvd.
Room 8184, MSC 9663
Bethesda, MD 20892
Tel:1-866-615-6464
www.nimh.nih.gov/publicat/index.cfm

National Alliance on Mental Illness
Colonial Place Three
2107 Wilson Blvd.
Suite 300
Arlington, VA 22201
Tel: 1-800-950-6264
703-524-7600
www.nami.org

Mental Health America
2000 N. Beauregard St.
6th Floor
Alexandria, VA 22311
Tel: 1-800-969-6642
703-684-7722
www.nmha.org

National Library of Medicine
U.S. government online repository of articles published in peer-reviewed medical journals.

www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed

National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health
Access to abstracts of peer-reviewed articles concerning complementary medicine.

NCCAM Clearinghouse
P.O. Box 7923
Gaithersburg, MD 20898
Tel: 1-888-644-6226
301-519-3153
www.nlm.nih.gov/nccam/camonpubmed.html

ConsumerLab.com
Tests herbal and vitamin products for purity and posts the results on the Web.

www.consumerlab.com

Mental Health Net
Features thousands of resources on the Internet.

www.mhnet.org

Kids Health
Features physician-approved health information about children.

www.kidshealth.org

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American Association of Suicidology
American College of Physicians
American Group Psychotherapy Association
American Mental Health Counselors Association
American Psychoanalytic Association
Anxiety Disorders Association of America
Association for Academic Psychiatry
Brazilian Research Consortium on OCD Spectrum Disorders
National Association of Social Workers

REFERENCES

The following coding system is used to indicate the nature of the supporting evidence in the references:

[A] *Double-blind, randomized clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.
[A–] *Randomized clinical trial.* Same as above but not double-blind.
[B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.
[C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.
[D] *Case–control study.* A study in which a group of patients is identified in the present and information about them is pursued retrospectively or backward in time.
[E] *Review with secondary data analysis.* A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.
[F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.
[G] *Other.* Textbooks, expert opinion, case reports, and other reports not included above.

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