

CURRENT AND EXPERIMENTAL THERAPEUTICS OF OCD

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UNIQUE ASPECTS OF OCD PHARMACOTHERAPY

Obsessive-compulsive disorder (OCD) is a chronic disorder with substantial impact on quality of life (1) that affects 2% to 3% of the US population (2,3). Previously believed to be refractory to treatment, the symptoms of OCD are substantially reduced with the use of medications having potent effects on blocking the serotonin (5-HT) transporter. The response to serotonin reuptake inhibitors (SRIs) in OCD is somewhat unique compared to that in other mood and anxiety disorders, in that higher doses and a longer lag-time to therapeutic effect of SSRIs may be required, and a lack of response to other antidepressant/antianxiety agents in OCD is evident. Nevertheless, SRIs do not cure patients, and 30% to 50% remain treatment nonresponders; therefore, other pharmacologic approaches, augmentation strategies, and especially cognitive-behavioral treatments may become necessary. Recently, other more invasive treatment options have been studied in the refractory population as well. This chapter highlights the psychopharmacology of OCD, including the current state of the art and future directions. Cognitive behavioral treatments for OCD, which are also highly effective, are not extensively reviewed here.

DIFFERENTIAL DIAGNOSIS AND COMORBIDITY: IMPLICATIONS FOR THERAPEUTICS

Although the diagnosis of OCD is usually straightforward, presenting with classic obsessive and compulsive symptoms, sometimes OCD presents with atypical features. Con-

versely, other disorders may present with symptoms reminiscent of OCD. For example, the ruminations of depression, intrusive thoughts, or delusions of psychotic disorders, and stereotyped behaviors of developmental disorders, may mimic OCD. Thus, comprehensive clinical evaluation and careful differential diagnosis are essential.

Psychiatric comorbidity is the rule rather than the exception in OCD. Up to two-thirds of all patients with OCD have lifetime comorbidities (3,4). These comorbid conditions not only serve to cloud the diagnostic picture, but also can influence the selection of optimal treatments.

The prevalence of obsessive-compulsive symptoms in schizophrenic patients has been estimated to range from 7.8% to 46.6% (5–7). A recent paper reported that in the early phase of the disorder, 14% of schizophrenic patients fulfilled criteria for a diagnosis of OCD (8). Atypical neuroleptics have been associated with both new onset and exacerbation of obsessions and compulsions, with numerous reports for clozapine (9) and less for risperidone. Treatment of OCD symptoms in schizophrenic patients may take into account this possible effect of atypical neuroleptics, and dosage reduction and/or SRI augmentation may be recommended (10).

The prevalence of OCD in patients with bipolar disorder has been estimated to be around 30% (11–12), half of whom had one or two other associated anxiety disorders (13); therefore, previous manic or hypomanic episodes and subthreshold hyperthymic characteristics should be evaluated and treated accordingly (14). Because SRIs may sometimes precipitate hypomanic or manic episodes in adults (15–17) and adolescents (18) without previous manic episodes, low initial doses, gradual dose elevation, and addition of mood stabilizers may be required.

IMPACT OF COMORBIDITY/SUBTYPES, OUTCOME MEASURES, AND RESPONDER CRITERIA

In evaluating treatment response in OCD, the patient population under study and measurement of response can signifi-

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cantly impact findings. For example, OCD patients who fail to respond to prior SSRI therapeutic trials may have only a 25% chance to respond to an additional SSRI trial (19). Likewise, patients with comorbid tics (20), delusional symptoms, or schizotypal personality disorder (21) may not respond to SSRIs, and may require neuroleptic augmentation strategies. OCD patients with neurological soft-signs may be poorly responsive to SSRIs (22). Also, specific OCD subtypes, such as hoarders, may be poorly responsive to SSRIs. Finally, related or OCD spectrum disorders share important features with OCD and may be comorbid with OCD, influencing treatment outcome (23).

TREATMENT RESPONSE

The degree of symptom resolution in response to treatment determines the need for dosage adjustment, augmentation, or switching to an alternative treatment. Treatment response may be assessed qualitatively via periodic clinical interviews or the regular use of validated scales such as the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) to quantify the ongoing severity of OCD symptoms. Approximately 60% of patients treated with SRIs experience at least a 25% to 35% decrease in symptoms in Y-BOCS (24), which is typically operationalized as a criterion for response.

Although the Y-BOCS score generally is an excellent gauge of symptomatic improvement, the overall change in quality of life also must be considered. The Y-BOCS does not reflect these quality of life issues, and may not be sensitive to subtle changes, such as going from 8 to 2 hours per day of rituals. The criteria set for response (i.e., 25% or 35% reduction in Y-BOCS, CGI improvement of 1 or 2, or a combination of the two) may markedly impact percentage of subjects who are considered responders in various trials, and thus studies that utilize different response criteria might yield very different response rates.

SEROTONIN AND DOPAMINE FUNCTION IN OCD

Evidence for serotonergic and dopaminergic function in OCD is discussed in detail elsewhere (see Chapter 112). Extensive research documenting the efficacy of SRIs has indicated that the antiobsessional properties of these drugs may be related to their 5-HT reuptake inhibition properties. Peripheral and central marker abnormalities have generally supported a proposed 5-HT hypothesis (25). Of note, in a subgroup of OCD patients, increased levels of CSF 5-hydroxyindoleacetic acid (5-HIAA) have been observed and a correlation has been found between response to treatment and a reduction of both 5-HIAA levels and platelet 5-HT concentration (26-27). The partial serotonin 5-HT_{2C} agonist *m*-chlorophenylpiperazine (*m*-CPP) has been found to

acutely exacerbate symptoms in a subgroup of OCD patients in some (28,29) but not all studies (30), and has generally demonstrated neuroendocrine blunting in these patients as compared to normal controls (29,31). Treatment with clomipramine or fluoxetine leads to cessation of this behavioral exacerbation and normalization of the neuroendocrine findings in response to repeat *m*-CPP challenge (32, 33). There is some evidence for linkage disequilibrium of the 5-HT_{1DB} receptor gene and OCD, with preferential transmission of the G allele to affected subjects (34). To date, a specific abnormality of the 5-HT system in OCD has not been identified and the strongest evidence in support of the serotonin hypothesis remains the preferential response to SRIs.

There is a debate regarding the nature of the SRI-induced changes to the 5-HT system. Administration of the SRIs results in an immediate inhibition of the 5-HT transporter, with the effect of increasing synaptic 5-HT; however, the full clinical response may not be seen for up to 8 to 12 weeks of SRI treatment. An understanding of the neuroadaptive changes that take place with treatment is helpful in clarifying the mechanism of action involved. It has been reported that desensitization of 5-HT₂ receptors is implicated in the antiobsessional effect of SRIs (35). Alteration of serotonin release in the orbito-frontal cortex has been found to occur only after 8 weeks of treatment (36). These adaptive changes seem to involve a reduction in the number of receptors and altered responsiveness of second messengers (37). There are many subtypes of 5-HT receptors, each having a distinct pattern of brain localization, with those expressed in basal ganglia and orbitofrontal regions of particular interest in the etiology of OCD (38).

There are complex structural and functional interactions between dopamine (DA) and 5-HT in the brain. Evidence implicating DA in the neurobiology of OCD is derived from a number of areas. In animal models, amphetamines have been shown to induce stereotypies that are viewed as compulsive behaviors (39). An association of postencephalitic Parkinson syndrome with obsessive-compulsive symptoms has been found (40). The comorbidity of Tourette syndrome and OCD is well described (41), as well as the association of a variety of other basal ganglia disorders with OCD. There is also evidence of DRD2 and DRD3 receptor gene polymorphisms in OCD (42).

SEROTONIN REUPTAKE INHIBITORS: ACUTE TRIALS

SRIs include clomipramine (Anafranil), fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa). Of these, fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram are "selective serotonin-reuptake inhibitors" (SSRIs), characterized by minimal affinity or pharmacologic action at receptor sites other

than the serotonin transporter. Clomipramine, on the other hand, is a tricyclic antidepressant (TCA). Thus, although clomipramine's serotonin-reuptake-blocking properties are similar to those of the SSRIs, it also has pharmacologically significant affinity for cholinergic and adrenergic receptors, thereby influencing its side-effect profile.

Although all SRIs block reuptake of serotonin presynaptically, there are other pharmacologic characteristics that distinguish these agents from one another, including differences in metabolism, half-life, protein binding, and effects on other neurotransmitter systems (43–45). All SRIs undergo hepatic metabolism and renal excretion. SRIs may be divided into those with active and those with inactive metabolites. For clomipramine, fluoxetine, and sertraline, which have active metabolites, the half-life of the daughter compound must be considered when estimating duration of effect after dosing. In general, measuring serum levels of SRIs and/or their metabolites has not been useful in determining effective dosage or predicting clinical response. Protein binding may influence levels of available drug in at least two ways: (a) if the patient is on other highly protein-bound medicines, competition can produce elevated levels of the SRI and/or the other agent, and (b) hypoproteinemia, as seen in chronic medical illness, malnutrition, or advanced age, can lead to higher concentrations of unbound SRI (i.e., the active form). There are subtle differences in the relative affinities of the various SRIs for monoaminergic reuptake sites, and more prominent differences between clomipramine and the SSRIs with respect to anticholinergic and antiadrenergic postsynaptic effects. These pharmacologic distinctions do not appear to have major consequences in terms of differential efficacy, but they do influence side-effect profile.

Case reports first suggested that obsessions might be successfully treated with clomipramine 30 years ago (46). Since then, controlled trials demonstrated clomipramine's efficacy in OCD. In the past decade, the introduction of the SSRIs has greatly increased treatment options (Table 114.1) (47–65).

The tricyclic SRI clomipramine, and the four selective serotonin-reuptake inhibitors fluoxetine, fluvoxamine, sertraline, and paroxetine, are currently approved by the FDA for the treatment of OCD in adults; three, clomipramine, fluvoxamine, and sertraline, are approved for treatment of OCD in children and adolescents. SRIs have also been found to be effective in treating other obsessive-compulsive spectrum disorders (23,66,67).

Although 65% to 70% of OCD patients have a clinically meaningful response to their first SRI treatment (68), with sequential trials as many as 90% of OCD patients may ultimately respond (69). Nevertheless, most patients are left with notable residual symptoms, perhaps with a 25% to 60% improvement (69). Although this improvement is clinically significant, patients may remain significantly impaired. These five SRIs have been demonstrated to be effective and well tolerated in OCD in short-term large

multicenter controlled trials (52,70–73). There is also evidence regarding long-term treatment response for some of these agents (71,74,75).

Clomipramine

Clomipramine is a tricyclic antidepressant that, in addition to being an SRI, is a potent norepinephrine (NE) inhibitor and has moderate dopamine (DA) receptor-blocking properties. It was the first medication found to be effective in the treatment of OCD and its efficacy has been firmly established over the past 30 years. The first two multicenter randomized controlled trials of clomipramine in the treatment of adult OCD were conducted in 1991 (52). CMI was administered in doses up to 300 mg per day for 10 weeks and resulted in reductions of 38% and 44% in OCD patients' total YBOCS scores compared to 3% and 5% in the placebo groups. These treatment effects were apparent at 6 weeks, and the YBOCS scores continued to improve over the course of the trial. Patients in the clomipramine versus placebo group were more likely to experience adverse events and discontinue treatment. Two notable adverse events on clomipramine were seizures (0.4%) and elevated aminotransferase levels (6.9%).

Fluoxetine

Fluoxetine, an SSRI, and norfluoxetine, its principal metabolite, have notably long half-lives. Early open trials suggested efficacy of fluoxetine in OCD (76,77). A large, double-blind placebo-controlled 8-week study of fluoxetine at three fixed doses (20 mg per day, 40 mg per day, and 60 mg per day) showed that the fluoxetine groups, combined, were superior to placebo in efficacy (72,78). Individually, the 40- and 60-mg dosage groups (but not the 20-mg group) were superior in efficacy to the placebo group. Fluoxetine was well tolerated and the dropout rate was low (<6%). In the multicenter study, which led to FDA approval, the same three doses of fluoxetine for 13 weeks were all significantly more effective than placebo in improving OCD (72). Defining response as a 35% improvement in total YBOCS score, response rates were 32.1%, 32.4%, and 35.1% for the 20-, 40-, and 60-mg groups, respectively, and 8.5% for placebo. Both obsessions and compulsions were found to respond to fluoxetine treatment independent of any antidepressant effect. Outcome on fluoxetine is unrelated to plasma levels of fluoxetine, norfluoxetine, or their sum (79).

Fluvoxamine

Several double-blind controlled studies have shown fluvoxamine to be effective in treatment of OCD (80–82). Perse and colleagues (80) reports on a multisite study that found fluvoxamine (100 to 300 mg per day) to be superior to placebo. In this study, 43% of patients receiving fluvoxamine

TABLE 114.1. CONTROLLED TRIALS OF SEROTONIN REUPTAKE INHIBITORS THERAPY FOR OBSESSIVE-COMPULSIVE DISORDER IN ADULT PATIENTS

Studies (Ref.)	Conditions	Results
Clomipramine (CMI) vs Placebo or Non-SRIs		
Karabanow, 1977 (47)	CMI vs placebo	CMI superior to placebo
Montgomery, 1980 (48)	CMI vs placebo crossover	CMI superior to placebo
Mavissakalin et al, 1985 (49)	CMI vs placebo	CMI superior to placebo
Jenike, 1989 (50)	CMI vs placebo	73% improved on CMI
Greist et al., 1990 (51)	CMI vs placebo	73% improved on CMI 6% improved on placebo
CMI collaborative group, 1991 (52)	CMI vs placebo	38%–44% decrease Sx with placebo 3%–5% decrease Sx with placebo
Thoren et al., 1980 (53)	CMI vs nort. vs placebo	CMI, but not nort., superior to placebo
Ananth et al., 1981 (54)	CMI vs amitriptyline	CMI superior to amitriptyline
Insel et al., 1983 (55)	CMI vs clorgyline	CMI effective, clorgyline not
Zahn et al., 1984 (56)	CMI vs clorgyline	CMI superior to clorgyline
Volavka et al., 1985 (57)	CMI vs imipramine	CMI superior to imipramine
Cui, 1986 (58)	CMI vs doxepin	78% improve on CMI 36% improve on doxepin
Lei, 1986 (59)	CMI vs imipramine crossover	CMI superior to imipramine
Zhao, 1991 (60)	CMI vs amitriptyline	95% improve on CMI 56% improve on amitriptyline
SSRIs vs Placebo or Non-SRIs		
Perse et al., 1987 (80)	Fluvoxamine vs placebo	Fluvoxamine superior to placebo
Goodman et al., 1989 (81)	Fluvoxamine vs placebo	Fluvoxamine superior to placebo
Goodman et al., 1990 (83)	Fluvoxamine vs desipramine	Fluvoxamine superior to desipramine
Chouinard et al., 1990 (85)	Setraline vs placebo	Sertraline superior to placebo
Jenike et al., 1990 (84)	Setraline vs placebo	Sertraline superior to placebo
Greist et al., 1992 (70)	Setraline vs placebo	Sertraline superior to placebo
Tollefson et al., 1994 (74)	Fluoxetine vs placebo	Fluoxetine superior to placebo
Montgomery et al., 1993 (78)	Fluoxetine vs placebo	Fluoxetine superior to placebo
CMI vs SSRIs		
Den Boer et al., 1987 (61)	CMI vs fluvoxamine	Comparable efficacy
Freeman et al., 1994 (103)	CMI vs fluvoxamine	Comparable efficacy
Pigott et al., 1990 (62)	CMI vs fluoxetine	Comparable efficacy
Koran et al., 1996 (63)	CMI vs fluvoxamine	Comparable efficacy
Lopez-Ibor et al., 1996 (102)	CMI vs fluoxetine	Comparable efficacy
Zohar et al., 1996 (64)	CMI vs paroxetine	Comparable efficacy

mine treatment responded after 6 weeks compared to 12% receiving placebo (defining response as much or very much improved on the improvement item of the Clinical Global Impression Scale). Of special interest, Goodman and associates (83) demonstrated the selective efficacy of SSRIs in OCD because fluvoxamine (up to 300 mg per day) was significantly more effective than the norepinephrine reuptake inhibitor desipramine in the reduction of obsessive-compulsive symptoms in an 8-week double-blind trial.

Sertraline

Although one early study did not find sertraline to be superior to placebo in the treatment of OCD (84), several subsequent studies have demonstrated its efficacy in OCD. Chouinard and associates (85) found sertraline (up to 200 mg per day) to be more effective than placebo on all out-

come measures in an 8-week trial. A large 12-week, multicenter, placebo controlled, double-blind trial of sertraline in three fixed doses (50, 100, or 200 mg per day), found sertraline at 50 and 200 mg per day to be significantly more effective than placebo, but the 100-mg dose was not more effective than placebo. Clinical outcome was not correlated with sertraline plasma levels (86).

Paroxetine

A large multicenter placebo controlled study of paroxetine in three fixed doses (20, 40, and 60 mg per day) found that the 40- and 60-mg doses were significantly more effective than placebo, but the lower dose (20 mg) was not more effective than placebo (71). There was a suggestion of a dose-response relationship, and paroxetine was well tolerated in the acute dose study phase.

Citalopram

Citalopram, the most selective of the SSRIs, has not been granted FDA approval in OCD. In a 24-week open pilot study of 29 OCD patients treated with citalopram, 76% had reduction in Y-BOCS scores of more than 50% compared to baseline, with most doses between 40 and 60 mg per day (87). In a 10-week single-blind study of 30 patients with OCD who underwent randomized treatment with fluvoxamine, paroxetine, or citalopram, there were no significant differences found between the three treatments, although the study was underpowered to detect significant differences between active treatments (88). Recent controlled treatment trials suggest efficacy in OCD (89).

Zimeldine

Although early research with zimeldine in OCD was promising, it has been withdrawn from use owing to several reports of Guillain-Barre syndrome occurring during treatment.

Venlafaxine

Venlafaxine, a serotonin/norepinephrine reuptake inhibitor, has not been systematically studied in controlled trials in OCD, but open pilot data suggest potential efficacy and the need for controlled trials (90).

SEROTONIN REUPTAKE INHIBITORS: SIDE EFFECTS AND DRUG INTERACTIONS

Side Effects

Efficacy must be balanced against side effects in choosing treatment options, and side-effect profile is magnified in OCD because the treatment is likely to be chronic. All SRIs can cause side effects attributable to their serotonergic action. Clomipramine, a TCA, is most apt to cause anticholinergic and antiadrenergic side effects, whereas SSRIs tend to cause fewer side effects mediated via nonserotonergic receptor systems (43–45,91–95).

TCAs such as clomipramine have a quinidine-like antiarrhythmic effect that slows intracardiac conduction (95). Although generally an issue only in patients with known cardiac disease, occasional adverse effects may be seen in patients with no documented pre-existing condition. Furthermore, in overdose, the cardiac conduction effects of TCAs lead to much greater toxicity than the SSRIs. This is important, because there is an increased rate of suicide attempts in OCD, especially when associated with comorbid disorders. TCAs have anticholinergic effects that can cause tachycardia, blurred vision, constipation, urinary retention, and confusion (44). Orthostatic hypotension may

occur as a result of α_1 -adrenergic antagonism (44). Last, clomipramine lowers seizure threshold (94).

SSRIs are relatively safe compared to TCAs. Few, if any, deaths have been reported following overdose with SSRIs. Although side effects are generally less severe, one may see agitation, anxiety, nausea, headaches, weight gain (over time), and sexual dysfunction (43). Although any of these side effects can contribute to noncompliance, sexual dysfunction is seen in as many as one-third of patients (92) but may not be readily reported unless the clinician specifically inquires about it. There are little systematic data on the treatment of SSRI-induced sexual dysfunction, but case reports and clinical practice have shown that effective interventions may include lowering the dose of SSRI or adding yohimbine (an α_2 -adrenergic antagonist), amantadine (a dopamine agonist), methylphenidate, cyproheptadine (an antihistaminic/antiserotonergic agent), buspirone, or sildenafil (69). There also exists a clinically significant discontinuation syndrome that occurs on abrupt discontinuation of an SSRI with short half-life (71).

Drug Interactions

Patients treated for OCD often take concurrent medications; therefore, potential drug interactions should be considered when selecting an antiobsessional agent. In addition to well-established drug interactions known to occur with clomipramine and other TCAs, individuals may also experience idiosyncratic reactions (91,93,95–99). Some medications interact with clomipramine by influencing its plasma concentration, whereas others potentiate clomipramine's side effects via synergy at relevant receptor sites. The hypotensive effects of clomipramine can be exacerbated by α -methyl dopa, β -adrenergic blockers, clonidine, diuretics, and low-potency antipsychotics. Quinidine and other class Ia antiarrhythmics as well as thioridazine, mesoridazine, and pimozide may add to cardiotoxic effects of TCAs. Common medications that have anticholinergic effects can synergize with TCAs to produce anticholinergic toxicity, including antihistamines, antiparkinsonians, low-potency antipsychotics, over-the-counter sleeping pills, and antispasmodics or antidiarrheals. Conversely, TCAs such as clomipramine can potentiate the effects of warfarin or block the effects of guanethidine.

SSRIs can participate in drug interactions as a consequence of effects on the hepatic cytochrome P-450 system (96–98). As each SSRI is metabolized by one or more isoenzymes of cytochrome P-450, they may either inhibit or induce the corresponding enzymatic activity, thereby affecting the metabolism of other drugs. Conversely, other medications can inhibit or induce the P-450 system, thereby modulating the metabolism of SSRIs. There is tremendous individual variation in P-450 effects. In addition, because SSRIs are highly protein-bound, this can lead to drug interactions

that do not involve the cytochrome P-450 system per se. For example, SSRIs can compete with warfarin, carbamazepine, and valproate for protein-binding sites, leading to increased levels of these agents, with accompanying adverse effects. In general, these interactions do not represent absolute contraindications to coadministration, but may require necessary adjustments to the dose of SRIs or other medications.

COMPARATIVE STUDIES OF THE SRIs

Efficacy

Although metaanalyses have suggested that clomipramine is more effective than the SSRIs, head-to-head comparisons of clomipramine and SSRIs show no particular edge in efficacy to any of these medications. Three metaanalyses consisting of comparisons of previously published data sets found clomipramine superior to SSRIs in OCD treatment efficacy (24,100,101). In the Greist metaanalysis, the three SSRIs fluoxetine, fluvoxamine, and sertraline, were found to have similar efficacy, whereas clomipramine was found to be significantly more effective. It is important to realize that the studies on which these metaanalyses were based did not include head-to-head comparisons and patient samples for clomipramine may have differed from those for the SSRIs. The clomipramine studies, which were generally conducted in an earlier time period, included SRI naive patients, while the SSRI studies included patients who had previously failed to respond to clomipramine or fluoxetine trials; thus, the SRI trials were likely to include more treatment-refractory patients.

A few studies have evaluated the relative efficacy of the SSRIs in double-blind, head-to-head comparisons. No difference was found in the rate of response to fluoxetine (40 mg per day) compared to clomipramine (150 mg per day) when response was defined as a 35% reduction in total YBOCS scores (102) but fluoxetine was found to be better tolerated. Two comparisons of fluvoxamine and clomipramine have found then to be equally effective and, again, the SSRI was better tolerated (103,104). A comparison of paroxetine and clomipramine also found equal efficacy with superior tolerability for the SSRI, which also had a lower discontinuation rate (105). Additional comparative studies would be helpful because these had small sample sizes that were underpowered to show significant differences between two active medications, and did not include comparisons among the SSRIs.

Tolerability

In the studies noted in the preceding, the SSRIs were seen to have somewhat fewer side effects than clomipramine, but this did not necessarily impact compliance; however, in the CMI trials, there were no other alternatives available, which might have impacted discontinuation rates. Clomipramine

has α -adrenergic, anticholinergic, and histaminergic effects and has quinidine-like cardiac properties that can increase the QTc interval. These effects can be a particular problem for OCD treatment, because it often requires doses higher than needed to treat depression. In a retrospective study comparing clomipramine and fluoxetine in the treatment of OCD, Jenike and colleagues (106) reported clomipramine treatment was associated with greater adverse events. For clomipramine, patients reported higher rates of sedation, dry mouth, nausea, dizziness, constipation, sweating, headache, and blurred vision. The adverse events reported for fluoxetine treatment were generally mild and transient. A metaanalysis of four large multicenter trials (52,70,72,86) found no difference in dropout rates owing to side effects: 8% for clomipramine, 10% for sertraline, 12% for fluoxetine, and 15% for fluvoxamine (24). Looking at the withdrawal rate for all causes, clomipramine had significantly fewer dropouts than the SSRIs despite having a greater rate of adverse events. However, as noted, this may be owing to the sample differences across studies discussed earlier, and lack of alternative treatment during the CMI trial. Typical tricyclic adverse effects were reported in the clomipramine collaborative study (52): dry mouth (80%), tremor (53%), dizziness (53%), sedation (49%), and male sexual dysfunction (41% of men). Fluoxetine was generally well tolerated in its multicenter study (72). The most commonly reported adverse effects were headache, nausea, insomnia, rhinitis, anorexia, dry mouth somnolence, anxiety, tremor, and diarrhea. There were significantly greater adverse effects with greater fluoxetine doses. In the sertraline study (24), the following adverse effects were reported significantly more frequently by the sertraline than the placebo group: diarrhea, insomnia, decreased libido, nausea, anorexia, ejaculation failure, tremor, increased sweating, and increased weight. Overall, 93% of the sertraline patients reported adverse effects with a correlation noted between higher dose and frequency of side effects; 77% of patients on placebo reported adverse effects. In the fluvoxamine study (70), the following adverse events were significantly more likely to be reported for fluvoxamine than placebo: insomnia, nausea, somnolence, asthenia, delayed ejaculation, nervousness, dry mouth, tremor, and anorexia. A recent review comparing controlled trials suggested that when compared with clomipramine, the SSRIs have equivalent efficacy and superior tolerability and lack anticholinergic side effects particularly (107).

Studies that compared clomipramine and an SSRI in double-blind, head-to-head comparisons, found the SSRIs to be better tolerated: Fluoxetine (40 mg per day) was better tolerated than clomipramine (150 mg per day) (102), as were fluvoxamine (103,104) and paroxetine, which also had a lower discontinuation rate (105). Efficacy and tolerability of clomipramine (100 to 250 mg per day) and fluvoxamine (100 to 300 mg per day) were compared in a double-blind, parallel group, randomized study (104). Both groups

showed steady improvement throughout the study; no differences were observed between the groups for any efficacy variable at any time and both clomipramine and fluvoxamine were equally effective in reducing OCD symptoms; they displayed differences in the profiles but not severity of the side effects.

LONG-TERM TREATMENT AND DISCONTINUATION

OCD is a chronic disorder; therefore, long-term treatment is often required. Although this research has methodologic limitations, data on long-term SSRI treatment (fluoxetine, sertraline, and paroxetine) suggests that efficacy is maintained and sometimes increases over time. Still more information is needed on the long-term efficacy and safety of SRIs in OCD treatment. SRIs have been proved effective in the acute treatment of OCD; double-blind substitution trials with clomipramine have shown that symptoms frequently recur after discontinuation of treatment (108,109).

A retrospective follow-up study of 85 patients with OCD reported that most of the patients treated with SSRIs for 1 to 3 years had maintained or increased symptom improvement (110). Two double-blind and/or placebo-controlled long-term SSRI continuation studies have reported continued efficacy and tolerability (74,75). Although valuable, these studies had no effective control group for the maintenance phase: Because only responders to an acute trial continued into long-term maintenance, there were only a handful of placebo patients in maintenance and there was no other control group. To date, no long-term, double-blind substitution trials have been published. An open-label discontinuation trial (111) followed 130 responders to 6 months of acute treatment with an SRI: clomipramine, fluoxetine, or fluvoxamine. This occurred for 2 years of treatment (or until they experienced a recurrence) with the same medication at the same dose, the same medication at half the dose, or no treatment. The study showed a superior therapeutic effect for both medication conditions compared to discontinuation of pharmacotherapy. One controlled, long term, double-blind substitution trial (71) has shown that paroxetine is superior to placebo in preventing OCD relapse during a 6-month discontinuation trial (which followed 12 weeks of acute treatment in a double-blind placebo-controlled paroxetine dose finding trial and 6 months of open-label paroxetine treatment). In addition, treatment effects appeared to be sustained and may have even increased over the time of the trial. In addition, following the double-blind discontinuation phase, subjects switched to placebo had a significantly greater rate of relapse, and time to relapse was significantly shorter on placebo versus paroxetine (71). One study suggested that long-term maintenance therapy might be provided with lower dosages of antiobsessional drugs, with a clear advantage for tolerability and compliance (112).

SRIs IN CHILDHOOD AND ADOLESCENT OCD

The clinical presentation of OCD in children and adolescents resembles that observed in adults (113). There has been increasing awareness of the frequency with which children and adolescents suffer from OCD (114). Clomipramine has been well studied in the treatment of OCD in this population. An 8-week multicenter double-blind study (115) found clomipramine to be effective and superior to placebo (mean Y-BOCS scores decreased by 37% versus 8%). These findings led to FDA approval of clomipramine for the treatment of OCD in children and adolescents. The side-effect profile in this sample included anticholinergic, antihistaminic, and α -adrenergic effects such as dry mouth, tremor, sedation, dizziness, sweating, and insomnia. No serious adverse events were reported; however, some patients were withdrawn owing to hepatic enzyme elevations and cardiac palpitations. Electrocardiographic monitoring should be undertaken because tricyclic antidepressants have the potential for being cardiotoxic (116).

Fluvoxamine is an FDA-approved SSRI for the treatment of pediatric OCD. In an 8-week open-label trial of fluvoxamine with adolescents (100 to 300 mg per day), the majority of patients showed significant improvement in their OCD symptomatology (117). The side-effect profile was similar to that reported in adults, including hyperactivity, anxiety, sedation, dizziness, headache, tremor, and nausea. A large ($N = 120$) double-blind placebo-controlled 10-week study of fluvoxamine (50 to 200 mg per day) with children and adolescents (ages 8 to 17) found the drug to be significantly superior to placebo (118). Side effects were described as mild; those that were more commonly reported in the fluvoxamine group included insomnia, agitation, hyperactivity, somnolence, and dyspepsia.

There have been four small prospective studies investigating the efficacy of fluoxetine in pediatric OCD. Three of these were open design (119–121). Riddle and co-workers (122) conducted a double-blind crossover trial of fluoxetine ($N = 14$; mean age 11.8; 20 mg per day, fixed daily dosing) and reported it to be superior to placebo as measured by CGI scores for global improvement. The most commonly reported adverse effects included insomnia, motor activation, fatigue, and nausea. In general, the side effects were reasonably well tolerated and did not result in withdrawal from the study, except for a 13-year-old boy who developed suicidal ideation in the third week of fluoxetine treatment. There were no significant changes in laboratory studies, EKG, weight, pulse, or blood pressure. Major limitations of the study were the small sample size and the fixed dosage.

In a retrospective chart review by Geller and colleagues (123), fluoxetine led to moderate to marked improvement in OCD symptoms in 74% of patients ($N = 38$); mean age 12.3). Relatively high doses of the drug were required, on average 50 mg per day (1.0 mg/kg per day). Long-term

TABLE 114.2. CONTROLLED TRIALS OF SEROTONIN REUPTAKE INHIBITOR THERAPY FOR OBSESSIVE-COMPULSIVE DISORDER IN CHILDREN AND ADOLESCENTS

Study (Ref.)	Conditions	Results
Flament et al., 1985 (125)	CMI vs placebo	CMI superior to placebo
Devaugh-Geiss et al., 1992 (115)	CMI vs placebo	37% decrease Sx on CMI 8% decrease Sx on placebo
Rapoport et al., 1980 (126)	CMI vs DMI vs placebo	No differences
Leonard et al., 1988 (127)	CMI vs DMI	CMI superior to DMI
Leonard et al., 1991 (109)	CMI substituted with DMI in 50%	18% on CMI relapsed
Riddle et al., 1992 (122)	Fluoxetine vs placebo	Fluoxetine superior to placebo
March et al., 1998 (124)	Sertraline vs placebo	Sertraline marked improved 42% vs 26% placebo
Riddle et al., 2001 (124a)		

efficacy was sustained over the follow-up period of, on average, 19 months. Fluoxetine was generally well tolerated and adverse effects were less marked than those associated with clomipramine. Despite this apparent tolerability of high doses, it has been recommended that, for children, an appropriate starting dose of fluoxetine is 10 mg per day or less (122).

The FDA has also approved sertraline for the treatment of child and adolescent OCD, which has been shown to be safe and effective in this population (124). In a randomized, double-blind, placebo-controlled trial, 107 children aged 6 to 12 years and 80 adolescents aged 13 to 17 years were randomized to receive either sertraline titrated to a maximum of 200 mg per day (53 children, 39 adolescent) or placebo (54 children, 41 adolescents). After 12 weeks, 42% of the patients receiving sertraline and 26% of those receiving placebo were very much or much improved on CGI ratings. The incidence of side effects was similar to that reported in adults; sertraline appears to be a safe and effective antiobsessional agent in children and adolescents.

In an open-label trial, the adverse effects and potential clinical efficacy of citalopram (10 to 40 mg) were examined in 23 children and adolescents (aged 9 to 18 years). After 10 weeks, over 75% of these youths showed a moderate or marked improvement and adverse effects appeared to be minor and transient, suggesting that citalopram might be well tolerated in children and adolescents (Table 114.2) (128).

Recent reviews on the treatment of children and adolescents with OCD suggest that adjunctive interventions including parent case management education and specific cognitive-behavioral should be considered in the majority of cases.

BEHAVIOR THERAPY AND PHARMACOTHERAPY

Prolonged exposure coupled with response prevention is a key element of behavior therapy for OCD. Exposure in-

volves prolonged confrontation with stimuli that provoke obsessional thoughts or compulsive behaviors. Patients agree not to engage in their usual ritualistic behavior or cognitions and to remain in the situation until their discomfort wanes. Homework is generally prescribed outside the therapist contact. Success rates vary from 50% to 80% (129). Some studies suggest that up to 90% of patients have achieved clinically significant benefits from behavior therapy (130). Generally, 70% to 80% of these patients maintain their acute gains at 1-year follow-up (131).

Intensive behavior therapy over 3 weeks has produced promising results, even in a very symptomatic group. Foa and colleagues (132) reported that 51% of patients experience at least a 70% drop in symptoms, with 35% experiencing a 31% to 69% reduction. These gains are generally (75%) maintained at 12-month follow-up. It is often difficult to arrange such extensive exposure in an outpatient setting, however. Recent results in one trial suggest that providing this treatment in a group setting may be effective and cost effective (133). Relapse prevention programs have proved beneficial in maintaining the gains of acute treatment (134).

Comparisons

A metaanalysis comparing behavioral treatments and SSRIs in OCD involved 77 studies in 4,641 patients. Effect sizes for behavior therapy were not significantly different from those of the SSRIs. There were also no significant differences between the SSRIs, although CMI appeared to have some increased efficacy but not sufficient enough to warrant favoring it over other SSRIs given its side-effect spectrum and the dangers associated with overdose (135). The choice between these two modalities is often dominated by the relatively limited availability of behavioral therapists and by patient preference. Up to 25% of individuals refuse behavioral therapy, whereas others prefer a nonpharmacologic treatment. A computer program offering behavior therapy via 12 computer-controlled interactive phone calls was found effective in over two-thirds of the patients (136).

In clinical practice, a combination of pharmacotherapy and behavioral therapy is often employed, although available research is not yet clear on potential benefits of combined medication and behavior therapy, either on response or relapse prevention.

TREATMENT-RESISTANT OCD: CLINICAL AND BIOLOGICAL PREDICTORS OF NONRESPONSE

It has been recommended that a minimum of 12 weeks of SRI treatment is needed to evaluate treatment response. Long-term trials have also noted continued improvement beyond this period.

The relationship between plasma levels of the SSRIs and treatment outcome in OCD is unclear. Studies on fluoxetine and sertraline indicated that plasma levels correlated with dosage but there was no evidence of a concentration—response relationship (75,137). It was reported that brain levels of fluoxetine and fluvoxamine reach steady state after 6 months and 1 month, respectively, and correlate with plasma levels (138). Current research is investigating the connection between brain steady-state levels and treatment response.

The response of OCD to drug treatment is frequently partial and incomplete. Poorer outcome has been associated with the presence of compulsions, the chronicity of the illness, and a continuous as opposed to fluctuating course (139) as well as the coexistence of borderline, schizotypal, or avoidant personality disorders (140). Depression is the most common comorbid diagnosis with OCD. The presence of concurrent depression at the start of treatment was not found to predict whether SRIs were effective in reducing obsessive-compulsive symptoms (100). Hollander and associates (141) reported that select measures of serotonergic function may be useful in predicting response to SRI treatment in OCD. They found that nonresponders to SRIs were likely to experience worsening of OCD symptoms and to have a blunted prolactin response on being challenged with the partial 5-HT agonist *m*-chlorophenylpiperazine (*m*-CPP). Further work is needed in this area. Also, OCD patients with increased neurologic soft-signs, a measure of subtle neurologic dysfunction, had a worse response to SRIs (22).

AUGMENTATION STRATEGIES

Augmentation strategies play an important role in OCD pharmacotherapy for SRI partial and nonresponders, as 40% to 60% of patients with OCD will not respond to an adequate treatment trial of an SRI. Augmentation agents added to SRIs include both serotonin enhancers and agents

involving other neurotransmitter systems, which may contribute to the pathophysiology of OCD.

Serotonergic Enhancers

Pharmacologic agents with serotonergic properties have shown varying utility in augmentation of SRIs.

Buspirone

Buspirone, a 5-HT_{1A} agonist, has been reported effective in treating OC symptoms in augmentation to fluoxetine in some open-label studies (142,143) but not in a controlled study (144). A 10-week double-blind trial of buspirone addition to ongoing clomipramine treatment reported no significant further clinical improvement in OC symptoms (145). In a double-blind, placebo-controlled study adding buspirone to fluvoxamine-refractory OCD, buspirone was not found to be significantly better than placebo in reducing OCD symptoms (146).

Fenfluramine

D-L-Fenfluramine, an indirect 5-HT agonist, added open-label to ongoing SRI treatment led to improvement in OC symptoms in six of seven patients (147). D-Fenfluramine also has been cited as potentially effective in augmenting clomipramine in OCD (148); however, these agents have been removed from the market because of side-effect issues.

Tryptophan

Tryptophan, a 5-HT precursor, has shown varying degrees of effectiveness in case reports of SRI augmentation in OCD (68,149), but has been removed from the market because of side effects. 5-HTP has been reported helpful in anecdotal case reports.

Lithium

Lithium, which is thought to enhance presynaptic 5-HT release in the brain (150) and influence second messenger systems coupled to 5-HT receptors, was reported to improve OC symptoms in three out of four patients treated with open-label addition to ongoing fluoxetine treatment (151). However, in a 4-week double-blind study of lithium augmentation to 16 OCD partial responders on clomipramine, there was no further decrease in OC symptoms reported after lithium (152). In two double-blind, placebo-controlled trials of lithium, addition to ongoing fluvoxamine treatment in OCD nonresponders (2-week study [20 points] and 4-week study [10 points]), only a small statistically significant reduction in OCD symptoms was reported from the 2-week trial, but not from the 4-week trial (153).

Clonazepam

Clonazepam, a benzodiazepine with unique serotonin properties, has been efficacious in augmentation to SRIs in the patients with OCD in case series (154) and in a double-blind, controlled augmentation trial with fluoxetine or clomipramine (155).

Trazodone

Trazodone, a 5-HT₂ and α -adrenergic blocker with weak 5-HT reuptake properties, which has *m*-CPP as a minor metabolite, was recently reported effective in augmentation to various SRIs in five cases of refractory OCD (156).

Pindolol

Pindolol is a B-adrenergic blocker with 5-HT_{1B} and 5-HT_{1A} receptor antagonist activity. Recent reports indicate that adjunctive pindolol may shorten the latency to antidepressant response to SRIs (157); however, data in OCD patients are mixed. One study of pindolol augmentation to paroxetine in resistant OCD resulted in mild improvement (158), whereas another report found that pindolol did not shorten the latency of fluvoxamine antiobsessional response (159). Thus, the utility of pindolol in non-depressed OCD patients is in doubt.

Dopaminergic Agents

The dopamine system has also been implicated in the pathophysiology of OCD; therefore, it is potentially useful in augmentation studies. Dopamine antagonist/SRI combinations have been reported to be effective in OCD.

Haloperidol

In a double-blind, placebo-controlled study of OCD patients on fluvoxamine monotherapy, haloperidol augmentation was found to be significantly more effective than that of placebo, and 100% of patients with a concurrent chronic tic disorder (8/8) responded to ongoing fluvoxamine-haloperidol treatment (160).

Pimozide

Open case series have shown the effectiveness of pimozide/SRI combinations in OCD patients with and without comorbid tic-related disorders (161).

Risperidone

In an open trial of risperidone/SRI combination treatment, 87% (14/16) of patients with refractory OCD had substantial reduction in OC symptoms (162). In another open trial,

after the addition of risperidone, seven out of 14 patients had clinical improvement after failing to respond to SSRI treatment alone (163). Other cases of risperidone augmentation reported effectiveness in reducing OC symptoms in patients who had failed SRI trials (164,165). A chart review, including eight OCD patients treated with the combination of an SRI and risperidone, reported three (37.5%) patients much or very much improved in OCD symptoms (166).

Olanzapine

Case series (167,168) and open-label trials (169) have reported benefits of adding titrated doses of olanzapine (10 or 15 mg per day) to an SSRI in refractory OCD patients. Thus, olanzapine might also be considered in the augmentation of severe forms of OCD, although careful monitoring of the potential interaction with SSRIs is suggested because this combination may produce idiosyncratic effect on plasma levels.

GABA/Second Messenger Systems

Gabapentin, a γ -aminobutyric acid (GABA) analogue, was reported to improve OC symptoms in 5/5 partial responders in a 6-week pilot study of fluoxetine augmentation within 2 weeks of treatment (170). In an open-label augmentation trial of SRIs with inositol, a precursor in the phosphatidylinositol cycle, 3/10 refractory OCD patients reported clinically significant responses on the CGI improvement scale (171); therefore, agents affecting other neurotransmitter or second messenger systems may play a role in augmentation strategies.

NOVEL PHARMACOTHERAPIES

Some individuals with OCD remain refractory even to augmentation strategies. For them, alternate pharmacotherapy may provide relief.

Intravenous Clomipramine

Intravenous clomipramine was first reported successful in treating obsessive symptoms in 1967 (46). A review of the literature found over 100 cases of successful treatment with intravenous clomipramine (172). In a double-blind, placebo-controlled trial of intravenous versus oral pulse loading of clomipramine in 15 OCD patients, six of seven patients treated with intravenous clomipramine were responders compared to one of eight patients with oral clomipramine (4.5 days after pulse loading), suggesting greater immediate improvement with intravenous pulses (173). This may be owing to avoidance of the first-pass liver metabolism of clomipramine, resulting in a greater clomipramine/desmethyl clomipramine ratio, more potent central 5-HT ef-

fects, and fewer side effects. The superiority of the intravenous route compared to the oral one has been reported in a placebo-controlled study (174). After 1 month of intravenous clomipramine (doses up to 250 mg per day) 58% of 21 patient nonresponders to oral administration randomized to receive intravenous clomipramine showed a marked clinical improvement rated by both CGI and Y-BOCS, without serious adverse events.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs), which block the catabolism of serotonin as well as norepinephrine and dopamine, have been reported successful for refractory OCD in some but not all studies. Case reports of successful treatment are available for iproniazid (175) and most substantially for phenelzine, which was one of the first pharmacologic agents tried for OCD. These reports primarily combined phenelzine with other medications (176–178). However, in a 10-week placebo-controlled comparison trial of fluoxetine versus phenelzine in 54 patients with OCD, patients treated with fluoxetine significantly improved more than those in the phenelzine or placebo groups, except for a subgroup of patients with symmetry obsessions who responded to phenelzine (179).

Serotonergic Agents

Buspirone monotherapy was reported to be ineffective in an 8-week open trial of 14 OCD patients (180) and Hewlett's survey found seven reported successes and 21 reported failures (172). Trazodone has been found successful in both cases and open trials of comorbid depression with OCD (181–183); however, it was found ineffective in reducing OC symptoms in a double-blind, placebo-controlled trial (184). The first treatment response to tryptophan was described in seven patients with OCD (185), with no further controlled studies. The role of other serotonergic agents in treating OCD including 5-HT₃ agonists (ondansetron) and 5-HT₂ agonists requires further research.

Noradrenergic Agents

The noradrenergic system has also been explored as a novel individual pharmacotherapy in OCD. A case report of clonidine, an α -2-agonist, documented improvement in OCD (186). Intravenous clonidine was reported to markedly reduce obsessions in six OCD patients (187). However, in a double-blind controlled crossover trial of clomipramine, clonazepam, and clonidine in 28 OCD patients, clonidine was found ineffective in reducing OCD symptoms (188).

Stimulants and Dopamine Releasers

Although most attention has focused on the blockade of dopaminergic receptors in OCD, there are also reports that

agents that release dopamine and dopamine receptor agonists may also have efficacy in OCD. Insel and associates (189) reported that two patients treated with amphetamines (10 to 20 mg) achieved a "persistent benefit" for a period of several weeks. He reported an additional two patients treated with "low-dose" amphetamines for several months who reported a decrease in obsessional symptoms. Ceccherini-Nelli and Guazzelli (190) described three cases of OCD with concurrent depression responding to the dopaminergic agonist bromocriptine (15 to 30 mg). These reports must be reconciled with reports that chronic administration of methylphenidate and amphetamine may induce ritualized behaviors and other OCD-like symptoms (191,192).

There are seven cases of reported improvement and one reported failure on chronic dopaminergic agonists. In a survey by Hewlett (172), five of 28 subjects (19%) achieved a good response with chronic amphetamine. Neither of these two patients treated with bromocriptine had any improvement. Bupropion, which inhibits dopaminergic reuptake, was associated with 15 failed treatments.

The OCD-like behaviors induced by chronic amphetamine may represent stereotypies, or complex tics, rather than compulsions that are performed to reduce anxiety. Clomipramine is a potent inhibitor of dopamine uptake and is antiobsessional. Conceivably, the response to low-dose neuroleptics in OCD may stem from their effects on blocking presynaptic dopamine D₂ receptors, increasing dopamine release (190).

Benzodiazepines

Case reports of clonazepam have also shown its efficacy (172,193). In a double-blind crossover trial, 40% of the patients who had failed clomipramine treatment had clinically significant responses to clonazepam treatment, and clonazepam was significantly more effective than clomipramine during the first 3 weeks of treatment (188). However, a double-blind multicenter placebo-controlled trial of clonazepam demonstrated no efficacy (194). Other benzodiazepines, such as alprazolam, have also not shown efficacy in treating OCD (195).

Anticonvulsants

There are three case reports of significant response to non-benzodiazepine-related anticonvulsants (two of whom had clinical epilepsy) all with carbamazepine, and 23 treatment failures (172). Two patients with OCD and clinical epilepsy responded to clonazepam treatment (196); however, clinical experience with anticonvulsants may be more positive. Two of 12 patients (17%) at two sites had successful trials of carbamazepine, and six of 26 patients (23%) at three sites had positive outcomes with sodium valproate (172).

Gonadal Steroids

There have been six reported cases of improvement associated with antiandrogen treatment, four of which were menstrually related, and one menstrually related improvement with an anovulatory medication (172). Only one antiandrogen failure has been reported, and one failure of estrogen treatment alone. An open trial with flutamide, an androgen receptor antagonist, in eight OCD patients, demonstrated a lack of response (197). None of the OCD centers has reported using this modality in treating OCD. As such, this treatment has not been well studied. In practice, the feminizing effects of these treatments in males limit their use in this population. In females, it is unclear whether treatment efficacy, if present at all, is limited to specific phases of the menstrual cycle. This treatment is unlikely to become a mainstream therapy for OCD.

Second Messenger System Agents

Agents that affect second messenger systems may also be effective in OCD. In a 6-week double-blind controlled crossover trial of inositol versus placebo in 13 OCD patients, YBOCS scores with inositol treatment were significantly lower than scores when on placebo (198).

Peptides

The role of peptide hormones has been studied in OCD. In one study, elevated CSF levels of oxytocin were found in a subtype of OCD patients compared to Tourette syndrome patients and controls, and levels were correlated with OCD severity, suggesting a possible role for oxytocin in the neurobiology of OCD (199). Oxytocin is a hormone released by the posterior pituitary that regulates uterine and lactiferous duct contraction. It has been implicated in certain ritualized behaviors and the extinction of active avoidance behavior in animals (200). In all, there have been three reported cases of improvement with chronic intranasal oxytocin and 12 failures (172–201). There have been no reports of improvement with vasopressin; however, this medication has not been administered chronically. None of eight patients at two OCD sites improved with oxytocin treatment. Although experience is limited with this modality, it does not appear to be a promising treatment.

Opiates

Warneke (202) reported that oral morphine in doses of 20 to 40 mg every 5 to 8 days produced marked benefit in five very severe cases of OCD. In contrast, naloxone has proved unsatisfactory and controversial (203,204). Tramadol, an analgesic that binds to opioid receptors and inhibits the reuptake of norepinephrine and serotonin, has been reported to produce a significant decrease in Y-BOCS scores

in a 6-week open-label study in seven treatment refractory OCD patients (205). Controlled trials are required, although it has low abuse potential, low physical dependency, and mild tolerance.

AUTOIMMUNE TREATMENTS

Autoimmune mechanisms may also play a role in at least a subtype of patients with OCD, particularly those who manifest a sudden onset of OCD symptoms following infection by group A B-hemolytic streptococci. Studies with oral penicillin were not found to be effective in such patients (206). Plasmapheresis and intravenous immunoglobulin (IVIG) have been reported effective in case studies (207). Recently, both IVIG and plasma-exchange groups were associated with significant improvement at 1 month in 30 children with infection-triggered exacerbations of OCD or tic disorders who received IVIG, plasma exchange, or placebo (208).

INVASIVE PROCEDURES

Finally, novel nonpharmacologic treatments may also play a role in treating some OCD patients. Right prefrontal repetitive transcranial magnetic stimulation has been shown to significantly decrease compulsive urges, compared to nonsignificant increases in urges with stimulation to midoccipital (control) areas and a nonsignificant reduction of urges in left lateral prefrontal areas (209). Further studies are warranted. Recent work with vagal nerve stimulation, deep brain stimulation, and various forms of neurosurgery suggest promise, but require controlled trials.

Patients who have failed all pharmacologic and behavioral treatments (and probably ECT) may be candidates for neurosurgical treatments of OCD (210). Various procedures in intractable cases have been successful, with 25% to 30% of patients experiencing significant benefit without undue side effects. The most common current neurosurgical procedure is cingulotomy, either performed via craniotomy or with the γ -knife procedure. In a United States trial, 18 patients underwent cingulotomy. At follow-up 2 years later, 28% met conservative criteria as responders, with 17% more meeting criteria as partial responders (210). Neurosurgery should be considered for a small percentage of truly refractory patients.

OCD SPECTRUM DISORDERS

An OCD spectrum has been proposed, consisting of various disorders that overlap with OCD in several features, including clinical symptoms (repetitive thoughts and behaviors),

course of illness, comorbidity, family history, neurobiology, and treatment response (selective efficacy of SSRIs) (25).

Three key clusters of disorders have been identified: (a) disorders with preoccupation with body image, body weight, or body sensations; (b) impulsive disorders in which repetitive behaviors are driven by pleasure; and (c) neurologically based disorders with repetitive behaviors. Clusters 2 and 3 are dealt with elsewhere in the volume. Here we focus on one disorder from the first cluster where there exist double-blind controlled pharmacologic data.

Body dysmorphic disorder (BDD), the distress of imagined ugliness, is a somatoform disorder in which patients are obsessed with an imagined imperfection or deformity in their appearance, and repeatedly check their appearance in mirrors or engage in cosmetic surgery to change their appearance. There is often poor insight or delusional conviction, and secondary depression and social phobia.

A recent double-blind crossover trial compared the SRI clomipramine to the noradrenergic reuptake inhibitor desipramine (DMI) (8 weeks of each phase) in 40 BDD patients (211). Desipramine, the active control, was chosen to control for nonspecific antidepressant and antidepressants, and because it has a similar side-effect profile to CMI, enhancing the blind. The SRI CMI resulted in significantly greater improvement in all primary outcome measures of BDD severity than did DMI, and also improved measures of functional impairment to a significantly greater extent than did DMI. Subjects with delusional conviction regarding body defect improved on CMI but not DMI, and severity of delusional conviction improved with CMI. Thus, BDD, like OCD, but in contrast to other mood or anxiety disorders, demonstrates a selective efficacy to SRIs, but not to NRI treatment. The delusional conviction in BDD appears secondary to obsessive preoccupation, and also responds to SRI treatment.

CONCLUSION

In summary, SSRIs and the tricyclic antidepressant clomipramine are currently the first-line treatment for OCD, with the SSRIs' side-effect profile being more favorable than that of clomipramine. However, 40% to 60% of patients with OCD may not respond to an adequate treatment trial of an SRI. Furthermore, not all patients tolerate SSRIs, and there is often a time delay in seeing a full therapeutic response. Thus, other pharmacologic approaches to treating OCD have been investigated, and certainly combinations of pharmacotherapy and cognitive behavioral therapy are considered the treatment of choice. Augmentation and novel monotherapy strategies have been explored in refractory patients, with serotonergic enhancers, dopamine/serotonin antagonists, enhancers of second messenger systems, and GABAergic agents, with varying efficacy. Recently, im-

munomodulatory and invasive procedures have been explored as well, but require further study.

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