Fluvoxamine in the Treatment of Obsessive-Compulsive Disorder and Related Conditions

Wayne K. Goodman, M.D., Herbert Ward, M.D.,
Anita Kablinger, M.D., and Tanya Murphy, M.D.

The mainstay of the pharmacologic treatment of obsessive-compulsive disorder (OCD) is a 10- to 12-week trial of a potent serotonin reuptake inhibitor (SRI) at an adequate dose. Double-blind, placebo-controlled trials have established the anti-obsessive-compulsive (OC) efficacy of five different SRIs. One of the most thoroughly studied of these SRIs is fluvoxamine, the focus of this article. Fluvoxamine's pharmacologic and pharmacokinetic properties, its efficacy, and guidelines for its clinical use in OCD and related disorders are briefly reviewed. Potential drug-drug interactions are discussed and placed in clinical perspective. The management of common SRI-induced side effects is also addressed. Recent comparative studies suggest that fluvoxamine may be equivalent in efficacy to clomipramine, yet better tolerated. Fluvoxamine shows promise in the treatment of several so-called OC-spectrum disorders, but additional controlled trials are needed.

(J Clin Psychiatry 1997;58[suppl 5]:32–49)

The modern era in the pharmacotherapy of obsessive-compulsive disorder (OCD) began more than 25 years ago with the clinical observation that clomipramine, but not other tricyclic antidepressants, was effective in some cases of OCD.[1] Several astute clinician researchers[2] went on to suggest the effectiveness of clomipramine in OCD might be traced to its potency at blocking serotonin reuptake, whereupon the serotonin hypothesis of OCD was born. Since those early encouraging case reports, the anti-obsessive-compulsive (OC) efficacy of clomipramine has been confirmed in numerous double-blind, placebo-controlled trials.[3] In most studies, the response of OC symptoms to clomipramine has been independent of baseline severity of concurrent depressive symptoms. The preferential efficacy of clomipramine over weaker blockers of serotonin reuptake has also been substantiated, lending support to the view that serotonin plays a pivotal role in the mechanism of action of anti-OC agents. For example, in double-blind, crossover trials, clomipramine was found more effective than the relatively selective norepinephrine reuptake inhibitor desipramine.[4,5] Nevertheless, a problem with concluding that the anti-OC efficacy of clomipramine is strictly related to its serotonergic actions is that desmethylclomipramine, a major metabolite of clomipramine, potently blocks reuptake of both serotonin and norepinephrine. In fact, during chronic treatment, desmethylclomipramine attains higher plasma levels than its parent compound.

The pursuit of the scientific question about the role of serotonin in the treatment of OCD, as well as interest in identifying alternatives to clomipramine, led to the testing of a newer generation of potent and selective serotonin reuptake inhibitors (SSRIs) in OCD. Double-blind, placebo-controlled trials have been conducted in OCD patients with the SSRIs fluvoxamine,[6] fluoxetine,[7] paroxetine,[8] and sertraline.[9] The status of potent SRIs vis-à-vis OCD and the United States market is summarized in Table 1. Unlike

Table 1. Approval Status and Dose Ranges of Serotonin Reuptake Inhibitors in Obsessive-Compulsive Disorder (OCD)*

	Indication			
Drug	OCD	Depression	Other	Dose[a]
Clomipramine	Yes	…	…	150–250 mg
Fluoxetine	Yes	Yes	Bulimia	20–80 mg
Fluvoxamine	Yes	…	…	100–300 mg
Paroxetine	Yes	Yes	Panic disorder	40–60 mg
Sertraline	Under review	Yes	…	50–200 mg

*As of October 1996 in the United States.
[a]Usual daily dose recommended for treatment of OCD.

From the Department of Psychiatry, University of Florida College of Medicine, Gainesville.

Presented at the closed symposium "Perspectives on Fluvoxamine Therapy," held March 2, 1996, in Orlando, Florida, and sponsored by Solvay Pharmaceuticals in conjunction with the Medical University of South Carolina, Department of Psychiatry and Behavioral Science through an educational grant from Solvay Pharmaceuticals, Inc.

This work was supported, in part, by NIMH grants MH45802 (W.K.G., Principal Investigator) and MH51846 (Dwight L. Evans, Principal Investigator), and by the State of Florida. The authors thank Donna Epting for help in preparing the manuscript. Leslie Brassloff, Pharm.D., of Solvay Pharmaceuticals, provided expert assistance in researching the literature.

Reprint requests to: Wayne K. Goodman, M.D., Department of Psychiatry, University of Florida College of Medicine, P.O. Box 100256, Gainesville, FL 32608.

clomipramine, none of these medications loses its selectivity for blocking serotonin reuptake in vivo. Also in contrast to clomipramine (and other tricyclics), these drugs lack significant affinity for histaminic, cholinergic, and α-adrenergic receptors, which are responsible for many of the untoward effects of clomipramine; i.e., sedation, weight gain; dry mouth, blurred vision, constipation; and orthostatic hypotension; respectively.

The remainder of this article will focus on fluvoxamine, its properties, and its use in the treatment of OCD. Studies of fluvoxamine in the so-called OC-spectrum disorders will be summarized briefly. (For an overview of the pharmacotherapy of OCD, see reference 10).

PROPERTIES OF FLUVOXAMINE

The structure of fluvoxamine maleate, a 2-aminoethyl oxime ether of an arylketone, is distinct from the tricyclic antidepressants. Although there is variability across published studies, fluvoxamine appears to be a more potent inhibitor of in vitro serotonin reuptake than fluoxetine, but less potent than paroxetine, sertraline, and citalopram.[11] Fluvoxamine retains its selectivity and potency for serotonin reuptake in vivo, and it has little in vitro affinity for the tested subtypes of adrenergic, serotonergic, muscarinic, or histaminergic receptors.[11] Accordingly, studies in animals and humans indicate that fluvoxamine has relatively few cardiovascular or anticholinergic effects.[11] Among the SSRIs, fluvoxamine is one of the weakest inhibitors of norepinephrine and dopamine reuptake.[11] The ratio between the potency of fluvoxamine for blocking reuptake of serotonin versus norepinephrine and dopamine is comparable to that of paroxetine and only exceeded by citalopram. How this selectivity for serotonin reuptake relates to clinical efficacy is unclear, however.

Fluvoxamine is well absorbed from the gastrointestinal tract, and absorption is not affected by food intake.[11,12] Peak plasma concentrations are reached 3 to 8 hours after oral intake. After a single oral dose of fluvoxamine, the half-life of plasma fluvoxamine is approximately 15 hours. Fluvoxamine is metabolized in the liver to inactive metabolites that are, in turn, excreted in the urine. One study[13] indicated that age had no effect on the pharmacokinetics of fluvoxamine, whereas another showed that plasma concentrations and elimination half-life were increased in the elderly.[11] The elimination half-life of fluvoxamine is increased in patients with hepatic impairment but is unaffected in those with renal impairment.[11] Plasma protein binding of fluvoxamine is 77% to 80%, which makes it less likely to interact with highly protein bound drugs. Available data suggest that fluvoxamine is not concentrated in breast milk.[14,15] As high doses of fluvoxamine were associated with possible adverse effects on the rat fetus in one study, this drug is rated Pregnancy Category C. While the risk of teratogenic effects with fluvoxamine seems small, its safety in human pregnancy has not been established.[11]

Inhibition of cytochrome P450 isoenzymes 1A2, 2C9, and 3A4 by fluvoxamine may slow the metabolism of some concomitant medications.[16] Fluvoxamine decreases the clearance and elevates the serum concentrations of alprazolam[17] and perhaps some other benzodiazepines,[18] including diazepam. Other drugs whose clearance may be decreased include warfarin, theophylline, propranolol, clozapine,[19] phenytoin, carbamazepine, some tricyclics[20] (including clomipramine[21]), methadone,[12] and some nonsedating antihistamines, terfenadine and astemizole.[11,18]

Elevated levels of terfenadine and astemizole have been associated with serious ventricular arrhythmias.[22] Ketoconazole and erythromycin, potent inhibitors of the 3A4 enzyme subfamily, have been associated with clinically significant adverse interactions when coadministered with terfenadine.[22] Although fluvoxamine is about 20 times less potent than ketoconazole in in vitro studies[23] and there have been no published accounts that fluvoxamine causes clinically significant increases in serum concentrations of terfenadine or astemizole, the coadministration of these agents with fluvoxamine is to be avoided. (A pharmacokinetic study of fluvoxamine and terfenadine was conducted in 20 healthy subjects, but the results are not available at the time of this writing.) The same cautionary note applies to nefazodone and other SSRIs (i.e., fluoxetine and sertraline) that inhibit the cytochrome P450 3A4 subfamily.[23] Drug interaction studies conducted with loratadine and medications that inhibit cytochrome P450 enzyme 3A4 (e.g., ketoconazole, erythromycin) have demonstrated increased plasma concentrations of loratadine; however, there were no clinically significant alterations in safety parameters (including QT_c intervals).[24] Several newer antihistamines, cetirizine (a metabolite of hydroxyzine)[25] and fexofenadine (a metabolite of terfenadine), may have less potential for interactions with fluvoxamine. No clinically significant drug interactions (including effects on QT_c interval) have been found for either cetirizine or fexofenadine when given with ketoconazole or erythromycin. Fexofenadine is predominantly renally excreted.[26]

Animal studies indicate that fluvoxamine lacks proconvulsive properties,[11] and a study in 35 epileptics found no change in their seizure frequency during fluvoxamine treatment.[27] There is one case in the literature, however, in which fluvoxamine appeared to lower seizure threshold.[28] Seizures have been reported with coadministration of fluvoxamine and lithium, but it is unclear whether these adverse events were due to interactions between these drugs.[29] Studies to date have not shown that fluvoxamine affects plasma lithium levels.[30] On the other hand, lithium addition, through a pharmacodynamic mechanism, may enhance the serotonergic effects of fluvoxamine and other SRIs.[31] In fact, lithium augmentation

of SSRIs, including fluvoxamine, is an established treatment for depression.[32] As long as signs of lithium toxicity or serotonin syndrome (e.g., myoclonus)[33,34] are monitored carefully, it does not appear that the risk of an interaction between fluvoxamine and lithium is large enough to warrant avoiding this combination altogether.[35] As with other SSRIs, fluvoxamine and monoamine oxidase inhibitors (MAOIs) should not be taken within 2 to 3 weeks of each other. According to the package insert for dexfenfluramine (Redux), combined use with SRIs is not indicated, apparently out of concern for possible development of the serotonin syndrome.[33,34]

As is true of other SSRIs, the therapeutic index (ratio of lethal to therapeutic dose) of fluvoxamine is high and the risk of death with intentional overdosage appears to be relatively low. There are few reports of death after fluvoxamine overdosage in the absence of concomitant medication or substances of abuse.[36] According to the manufacturer, worldwide exposure to fluvoxamine includes more than 37,000 patients in clinical trials and an estimated 4.5 million patients treated in foreign marketing experience (as of 1992). In this database, there are 354 cases of deliberate or accidental overdosage with fluvoxamine that resulted in 19 deaths. Of the 19 deaths, 2 were patients taking fluvoxamine alone, and the remaining 17 cases involved fluvoxamine with other concurrent medications. The highest reported nonlethal ingestion of fluvoxamine is 10,000 mg, which is equivalent to a 1- to 3-month supply.[37]

FLUVOXAMINE AS AN ANTIDEPRESSANT

Fluvoxamine was among the earliest of the SRIs to undergo testing. Clinical trials were initiated in 1974, and first marketing approval was obtained (in Switzerland) in 1983. It is available by prescription in 58 countries outside the United States, chiefly for the treatment of depression. A number of controlled clinical trials have been conducted in Europe and North America to evaluate the efficacy and safety of fluvoxamine as an antidepressant. In most published double-blind trials in depressed patients, fluvoxamine has been shown to be significantly better than placebo[38–41] and equal in efficacy to tricyclics such as imipramine[38,40,41] and clomipramine.[42,43]

STUDIES OF FLUVOXAMINE IN OCD

Early Studies

Formal testing of fluvoxamine in the treatment of OCD began in the United States in the late 1980s. In a single-blind study of fluvoxamine in 10 inpatients with severe OCD,[44] 6 were responders on the basis of a clinical rating of "much" or "very much improved" on a modified version of the Clinical Global Impressions scale[45] (CGI). Thus, patients rated as "somewhat improved" were classified as "nonresponders." Most of the patients in this study were previously refractory to adequate trials of other antidepressant medications. These encouraging findings were replicated by two double-blind studies[46,47] of fluvoxamine in outpatients with OCD.

In a study conducted at the University of Wisconsin, 16 OCD patients completed a 20-week randomized crossover trial comparing fluvoxamine with placebo.[46] Patients received study drug for 8 weeks, each arm separated by a 2-week placebo washout period. Fluvoxamine was found to be efficacious on several different measures of OCD. For example, marked clinical improvement in OCD was only associated with the active drug phase, with 9 (56%) of 16 patients classified as better during fluvoxamine treatment.

Similar findings were obtained in a parallel-groups design study conducted jointly at Yale and Brown.[47] Forty-two OCD patients were randomly assigned to 6 to 8 weeks of treatment with either fluvoxamine (up to 300 mg daily) or placebo. All patients had a principal diagnosis of OCD (according to DSM-III), but approximately one half the sample had coexisting major depression. The principal outcome measure for OCD was the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), a 10-item clinician-rated questionnaire (each item rated on a 5-point scale from 0 = "no symptoms" to 4 = "extreme symptoms," total score range = 0 to 40).[48,49] (This represented the first published trial using the Y-BOCS.) The Y-BOCS consists of five items on obsessions and five on compulsions that assess the time, interference, distress, resistance, and control associated with both subcomponents.

In the 9 fluvoxamine responders, the mean Y-BOCS scores at the conclusion of treatment were 42% below baseline ratings. This degree of improvement represented major gains in social and vocational functioning for these patients. The mean ± SD Y-BOCS score of this responder group at the end of the trial was 14 ± 7, which corresponds to a global severity in the mild to moderate range. Thus, these patients were much improved but not entirely free of symptoms. In fact, no patient had a Y-BOCS score of 0 at the end of the double-blind trial. Although statistically significant mean group effects of fluvoxamine on OC symptoms emerged after only 2 weeks of treatment, clinically meaningful changes were generally not apparent until after 4 to 6 weeks of treatment. In fact, of 7 patients that were considered only partial responders by Week 6, 5 converted to full responders after 2 additional weeks of fluvoxamine at Week 8. This observation led to the suggestion that longer durations of treatment might be required for OCD compared with depression. At present, the consensus among experts is that at least 10 to 12 weeks of treatment with an SRI is required to qualify as an adequate trial in OCD.

To further examine whether the serotonergic actions of fluvoxamine are relevant to its anti-OC efficacy, investigators at Yale and Brown compared fluvoxamine with desipramine in 40 outpatients with OCD.[50] After 1 week of

single-blind placebo, patients were randomly assigned to 8 weeks of double-blind treatment with either fluvoxamine or desipramine in doses up to 300 mg daily. As measured by reduction in total Y-BOCS scores, fluvoxamine was found to be significantly superior to desipramine in the treatment of OCD. Eleven (52%) of 21 patients treated with fluvoxamine for 8 weeks were responders (as measured by the CGI), compared with 2 (11%) of 19 who received desipramine for 8 weeks ($p < .01$, Fisher's exact test). The findings from this trial extended earlier findings that clomipramine was more effective than desipramine in patients with OCD, and thereby provided additional evidence that the serotonin reuptake properties of a medication are relevant to its anti-OC efficacy.[4,5]

In the aforementioned studies, the anti-OC response to fluvoxamine was independent of the presence or severity of coexisting depressive symptoms at baseline. In contrast to later large scale trials (discussed below), the designs allowed inclusion of patients with a range of severity in secondary depressive symptoms. In the placebo-controlled study by Goodman et al.,[47] there was no significant correlation between fluvoxamine-induced improvement in Y-BOCS scores and baseline ratings of depression (on the basis of the Hamilton Rating Scale for Depression[51] [HAM-D]). This experience with fluvoxamine in OCD parallels that of most studies that have attempted to distinguish the antiobsessional from the antidepressant actions of other antidepressants in OCD.[50,52] In all but one study of clomipramine in OCD,[53] coexisting depression was not a necessary condition for an antiobsessional response to occur. It should be noted, however, that when OC symptoms improve as a result of SRIs, so do depressive symptoms, if initially present at baseline. Sometimes depression may lift with SRI treatment without a corresponding response of OC symptoms, but it is highly unusual to see the converse, that is, improvement in OCD without improvement in depression.

Pivotal Trials

Efficacy. These initial positive findings led the manufacturer (data on file, Solvay Pharmaceuticals) to sponsor multicenter, double-blind, placebo-controlled trials of fluvoxamine in the treatment of OCD.[6] These pivotal trials were conducted at eight sites in the United States and involved 320 outpatients aged 18 to 68 years. (Although there were two studies of identical design, each at four sites, the data from both studies have been pooled for the purpose of this discussion.) After a 2-week single-blind placebo washout period, patients were randomly assigned to 10 weeks of either fluvoxamine or placebo under double-blind conditions. Patients were required to meet DSM-III-R criteria for OCD for at least 12 months prior to study entry. Only those with at least moderately severe OC symptoms (as measured using the National Institute of Mental Health [NIMH] OC Scale[54]) but minimal depressive symptoms (Hamilton Rating Scale for Depression score of 19 or less) were eligible. The mean Y-BOCS scores at baseline for the fluvoxamine and placebo groups were between 22 and 24, which corresponds to OC symptoms in the moderately severe range. Patients with a history of schizophrenia, bipolar disorder, organic brain syndrome, mental retardation, Tourette's syndrome, panic disorder, agoraphobia, eating disorders, borderline or schizotypal personality disorder, or a history of significant substance abuse were excluded. No concomitant psychotropic medications were permitted during the study with the exception of occasional chloral hydrate (500 mg) or lorazepam (1 mg) for insomnia. The dose of fluvoxamine was titrated up to a maximum of 300 mg daily. The primary outcome variables used in the study were the mean change scores from baseline on the Y-BOCS and the NIMH OC Scale. In addition, the Global Improvement item on the Clinical Global Impressions scale was used as a categorical measure to define responders (i.e., "much" or "very much improved"). Patients who were rated as somewhat improved on the CGI were counted as nonresponders. An intent-to-treat sample, defined as all randomized patients having at least one post-baseline assessment, was used for all efficacy analyses.

One hundred twenty-one (76%) of the patients assigned to fluvoxamine completed the study compared with 139 (87%) who were taking placebo. Analysis of the intent-to-treat sample revealed significantly greater mean improvement from baseline for the fluvoxamine-treated group than for the placebo-treated group on both the Y-BOCS and the NIMH OC Scale. By the end of Week 10, Y-BOCS scores decreased by 23% in the fluvoxamine-treated group compared with only 7% treated with placebo. As in previous studies of SRIs in OCD,[47] examination of Y-BOCS subscale scores disclosed equivalent reductions in severity of obsessions (sum of items 1–5) and compulsions (sum of items 6–10) in patients who improved while taking fluvoxamine. Significant reductions in total Y-BOCS scores occurred as early as Week 6 in the fluvoxamine group. The mean Y-BOCS score at Week 10 among fluvoxamine completers was 17.8, which is still in the moderate range of severity. On the other hand, among the patients classified as responders on the CGI, the mean Y-BOCS score was 20.2 at baseline and 11.8 at endpoint, placing these patients in the mild range of overall symptom severity. Forty-three percent of the fluvoxamine group were considered responders compared with 11% of the placebo group. The placebo responders had significantly lower baseline Y-BOCS scores (mean = 17.2) compared with the placebo nonresponders (mean = 24.1).

The mean daily dose at Week 10 was 249 mg for fluvoxamine and 258 mg for placebo. As in other studies of SRIs in OCD, there was no significant correlation between plasma fluvoxamine levels and response. Previous

studies of fluvoxamine in OCD or depression also failed to find a relationship between plasma levels and outcome.

Side effects. Adverse events were responsible for 24 (15%) of the fluvoxamine dropouts and 7 (4%) of the placebo dropouts. Only 6% of the side effects reported on fluvoxamine were rated as severe. The side effect profile of fluvoxamine was similar to that seen in clinical trials of other SSRIs. Asthenia, nausea, dry mouth, insomnia, nervousness, somnolence, tremor, abnormal taste, decreased libido, and abnormal ejaculation were significantly more common with fluvoxamine. Nausea was reported in nearly one third of the fluvoxamine-treated patients, but it was mild or moderate in the vast majority of cases, tended to abate over time, and led to study termination in only 1 case. Delayed or absent ejaculation was reported in 18% of the males receiving fluvoxamine and in none of the placebo group; anorgasmia emerged in 3.1% of the females taking fluvoxamine and in none taking placebo.

Predictors of outcome. Data from this study were used to address several important clinical questions about predictors of outcome. First, can one predict based on early response to medication whether or not a patient will later experience significant improvement? It would be preferable to spare patients from many more weeks of unbeneficial medication treatment if they could be identified as nonresponders in the first few weeks of a trial. After the second week of the pivotal trial, approximately 10% of the fluvoxamine-treated patients converted to responder status during each successive 2-week period up to Week 10. However, relatively large Y-BOCS changes (nearly 28% reduction) at Weeks 4 and 6 were needed to predict response outcome at Week 10 with 95% confidence. As the predictive power of changes at Weeks 4 and 6 is low, a trial with fluvoxamine (and perhaps with other SRIs) should be extended to the full 10 to 12 weeks in all cases unless untoward side effects prevent doing so.

Second, how does previous history of nonresponse to an SRI affect the odds of responding to a different SRI? In the pivotal trials, 6 (19%) of 31 patients who had previously failed trials of clomipramine or fluoxetine responded to fluvoxamine. This is compared with a 50% (63 of 126) response rate to fluvoxamine among patients who were not previously treated with an SRI. Thus, as expected, history of SRI nonresponse does predict a diminished rate of response to a subsequent SRI trial. Nevertheless, this reduced response rate (approximately 2 of 10 patients) is still about double that expected from response to placebo (approximately 1 of 10).

Third, can other clinical or demographic variables, such as comorbidity, age, gender, or OC symptom typology or severity, help predict outcome? In the multicenter trials of clomipramine, of the demographic or clinical variables that were examined, only age at onset showed an association with outcome.[55] Patients who developed OCD later in life had a better chance of responding to clomipramine than those who became ill earlier, independent of duration of illness. The pivotal trials of fluvoxamine in OCD failed to find any significant correlation between fluvoxamine response and baseline clinical characteristics. In other studies, comorbid schizotypal personality disorder appears to be associated with a worse prognosis for OCD patients being treated with SRIs.[56] Based on a retrospective analysis of patients treated at Yale, personal history of a chronic multiple tic disorder (discussed later) may signal a poor response of OC symptoms to fluvoxamine.[57] Because tics were exclusionary in these pivotal trials, the predictive value of this comorbid condition could not be evaluated.

Comparison With Other SRIs

With several SRIs now available in the United States, clinicians are looking for information on how to decide which agent they should prescribe for OCD. In the general case, the relative efficacy, pharmacokinetics, and side effect/safety profile are all weighed in arriving at recommendations for use. Increasingly, cost may determine whether the patient can afford taking the medication or if it will be included in the formulary of the hospital or health maintenance organization. In the individual case, clinical variables such as medical condition and prior psychotropic history are taken into consideration prior to prescribing a particular drug. There is presently no reliable information on how to predict which of the SRIs established in OCD will be best suited to a particular patient with OCD. The discussion herein will be limited to consideration of comparative efficacy and tolerability.

To date, few direct comparative trials of SRIs in OCD have been published. In one of the first studies of its kind,[58] fluoxetine and clomipramine were found to have similar therapeutic efficacy. Although there were no significant mean differences in the efficacy of fluoxetine versus clomipramine, some individual patients showed differences in their response to the two drugs. Individual patients who showed more than a 20% difference in improvement on the Y-BOCS between the two drug treatments were labeled by the authors as having a preferential drug response. Using this criterion, 5 patients were preferential clomipramine responders, 2 were preferential fluoxetine responders, and 4 had similar responses to clomipramine and fluoxetine.

Subsequently, several meta-analytic studies[59,60] appeared in the literature that suggested that clomipramine's anti-OC efficacy was superior to that of the SSRIs. However, if one contrasts the U.S. multicenter clomipramine study with the pivotal trials of fluvoxamine, it becomes evident why comparison of the effect sizes might be misleading and the superiority of clomipramine might be more apparent than real. As indicated earlier, the data from the pivotal fluvoxamine trial suggest that patients with a history of SRI nonresponse are less likely to respond to a

second SRI trial compared with those without previous SRI exposure. Whereas 19% of the fluvoxamine patients had already failed a previous trial of an SRI, none of the patients participating in the earlier clomipramine trials was a known SRI nonresponder, as no other SRIs were yet available. In contrast, subsequent multicenter trials of SSRIs have all included patients who previously failed while taking one or more SRIs. Other shortcomings of meta-analytic approaches in general[61] and as they pertain to OCD specifically[62] are discussed elsewhere.

Several earlier direct comparative trials of fluvoxamine and clomipramine suffered from methodologic limitations such as small sample size (N = 12)[63] or unblinded conditions.[64] The shortcomings notwithstanding, fluvoxamine and clomipramine were equally effective in these studies. More recently, fluvoxamine was directly compared with clomipramine in two larger double-blind studies with similar designs.[62,65] All subjects were adult outpatients with a principal diagnosis of DSM-III-R OCD uncomplicated by major depression. Patients were randomly assigned to either fluvoxamine (100–300 mg/day) or clomipramine (100–250 mg/day) for 10 weeks.

In the study by Freeman et al.,[65] 66 patients were studied at nine sites in the United Kingdom. At endpoint (Week 10), both the fluvoxamine- and clomipramine-treated groups showed significant improvement on all three outcome measures for OCD. Total Y-BOCS scores were decreased by 33% in the fluvoxamine groups and 31% in the clomipramine group. At no time point were there significant between drug group differences in effect on OCD. It should be noted, however, that baseline HAM-D ratings were significantly higher in the fluvoxamine group and that after 10 weeks, the change from baseline in HAM-D ratings was significantly greater for fluvoxamine compared with clomipramine.

The study described by Koran et al.[62] involved 79 patients at multiple sites in the United States. As reflected on the Y-BOCS, statistically significant improvement from baseline was apparent beginning at Week 2 for both treatment groups. As in the aforementioned study, there were no significant between group differences in OC symptom response at any time point. At Week 10, the mean decrease in Y-BOCS scores from baseline was 30.2% for fluvoxamine and 30.0% for clomipramine. The response rate (where responder was defined by a ≥ 35% reduction in Y-BOCS score) to fluvoxamine (44%) and clomipramine (38%) was also similar. In comparison with clomipramine, fluvoxamine was associated with significantly less orthostatic hypotension and dry mouth but significantly more insomnia, nervousness, and dyspepsia. The clomipramine and fluvoxamine groups did not differ in their dropout rate due to adverse experiences, and no serious adverse events were reported.

Several potential limitations of these studies need to be noted. The absence of a parallel placebo group does not allow calculation of the net (placebo-corrected) drug effect and, thus, raises questions about the adequacy of the trial. On the other hand, most other studies of OCD show a low placebo response.[66] Furthermore, the magnitude of change observed with fluvoxamine in the studies under discussion is comparable with that seen in most other studies in OCD. That the response to clomipramine was less than that reported in the pivotal trials conducted nearly a decade earlier could be explained by differences in the subjects under study (see earlier discussion). Koran et al.[62] acknowledge, however, that their sample size may have been insufficient to detect small differences in the efficacy of clomipramine and fluvoxamine.

How does fluvoxamine compare with other SSRIs with respect to side effect profile? There are no head-to-head comparison trials to turn to; however, Devane[18] recently compiled data from a number of different sources (i.e., controlled clinical trials, postmarketing surveillance, prescription audits, and case reports) to arrive at comparison of the safety and tolerability of SSRIs. As with other potent SRIs such as fluoxetine, nausea is common but usually tolerance develops rapidly. Although some reports suggested that nausea was more common with fluvoxamine, the weight of placebo-corrected evidence indicates that the incidence of nausea is no greater with fluvoxamine. Other common side effects of fluvoxamine include agitation, insomnia, daytime drowsiness, tremors, and delayed orgasm. Compared with the other SSRIs, fluvoxamine appeared to produce fewer sexual side effects.

Duration of Treatment, Maintenance Dosing, and Relapse Prevention

During long-term SRI treatment, most patients with OCD seem to maintain the gains first achieved during the acute drug trial.[67–69] Unfortunately, available studies suggest that the rate of relapse seen after discontinuation of medication is higher in OCD than that generally seen in depression. For example, Pato and colleagues[70] at the NIMH observed a relapse rate of nearly 90% within 2 months after abrupt discontinuation of clomipramine in 18 remitted patients. A desipramine substitution study[71] yielded a similar relapse rate. Whether a gradual taper of medication over a long period of time (e.g., 6 months or more), as is usually done in clinical practice, produces a lower relapse rate has yet to be tested in a controlled study. Both clinical experience and several published reports[68,72] suggest that patients with OCD can be maintained successfully at lower doses than those used to initiate a treatment response. Ravizza et al.[68] recently reported on a 2-year open-label follow-up study of 281 OCD patients who had received acute treatment with either clomipramine, fluoxetine, or fluvoxamine. For all three drugs, half-dose maintenance therapy was equal in efficacy to full-dose therapy. The relapse rate was 25% to 40% among patients who continued taking drug (either half- or full-dose),

whereas it was 77% to 85% among those who discontinued drug. A double-blind, placebo-controlled trial of fluvoxamine in relapse prevention is currently in progress. Future studies need to examine whether the addition of behavioral therapy may help curb the relapse rate after medication discontinuation.

Fluvoxamine in Children and Adolescents With OCD

Recent studies support the efficacy of SRIs in the treatment of elective mutism, depression, OCD, and pervasive developmental disorders in children and adolescents.[17,73–76] In an inpatient, open-label study of adolescents with OCD or depression, fluvoxamine significantly decreased symptom severity.[77] The mean daily dose was 200 mg (range, 100–300 mg). Side effects most commonly reported were insomnia (20%), anxiety, hyperactivity or excitement (15%), tremors (15%), nausea (15%), and dermatitis (10%). In this study, 2 debilitated patients with anorexia poorly tolerated the medication, 1 developed hallucinations, and 1 developed delirium.[77]

Riddle et al.[78] recently reported the findings of a double-blind, placebo-controlled, multicenter trial of fluvoxamine in 120 children and adolescents (aged 8–17 years) with OCD. Patients were randomly assigned to 10 weeks of either placebo or fluvoxamine at a dosage of 50 mg to 200 mg (mean dose = 155 mg). Fluvoxamine was found to be effective and well-tolerated. The most common side effects reported were insomnia, agitation, hyperkinesia, and dyspepsia. Only 4 subjects dropped out secondary to side effects. No clinically significant findings in laboratory or electrocardiogram (ECG) parameters were observed.

Behavioral activation was reported in both these studies, similar to findings in studies of fluoxetine in the treatment of OCD in children.[75] This side effect did not appear to be associated with a specific diagnosis or family history and tends to resolve with discontinuation or dosage reduction. In those patients where discontinuation of the SRI would result in relapse of OCD symptoms, some clinicians suggest adding a mood stabilizer.[75,79] In one case report, a 14-year-old with OCD developed Tourette's syndrome (TS) during fluvoxamine therapy.[80] Symptoms resolved when the medication was discontinued and returned with reintroduction of fluvoxamine.

FLUVOXAMINE IN THE TREATMENT-REFRACTORY PATIENT

After an adequate trial with an SRI, only 40% to 60% of OCD patients are significantly better, and even responders rarely attain a Y-BOCS score of 0. Consequently, there has been a great deal of interest in developing and testing therapies for partial responders and intractable cases. (For a review of biological approaches to the treatment-refractory patient with OCD, see Goodman et al.[81]) The principal pharmacologic approaches to the treatment-resistant OCD patient include changing to a different SRI or combining another medication with the current SRI. Although the emphasis of this paper is on pharmacologic approaches to OCD, behavioral therapy should be integrated into the overall treatment plan. A more detailed description of how to combine cognitive-behavioral therapy with pharmacotherapy can be found elsewhere.[82]

Several published reports indicate that prior treatment failure with one SRI reduces the chances of response to a different SRI, including fluvoxamine.[6,83] In the pivotal fluvoxamine trials described earlier, history of prior SRI nonresponse was associated with about a 50% reduction in response rate.[6] Nevertheless, it still seems worthwhile to try a different SRI if there has been no meaningful improvement after an adequate trial with one SRI; if there have been partial gains, a combination approach may be considered instead. Naturally, if the patient does not tolerate one SRI, it makes sound clinical sense to try a different SRI.

Before turning to combination approaches, the use of high dose strategies warrants some discussion. It has become almost axiomatic that OCD requires high doses of chemotherapy; however, until recently, there were scant empirical data supporting this prescribing practice. Fixed-dose trials suggest that somewhat higher doses of fluoxetine[7] and paroxetine[8] are required in OCD compared with depression. The relationship between dose and response for sertraline is not easily deciphered from a fixed-dose trial in OCD.[84] Notably, however, Byerly et al.[85] recently published a case report suggesting that higher than recommended (above 200 mg/day) doses of sertraline may be beneficial in some patients with treatment-refractory OCD. As we are unaware of any data to support the efficacy and safety of fluvoxamine in doses greater than 300 mg daily, a high-dose strategy cannot be recommended for this drug.

Fluvoxamine has been used as the SRI backbone in a number of combination trials in treatment-refractory OCD. The rationale for the majority of combination strategies has been to add agents to ongoing SRI therapy that may modify serotonergic function, such as tryptophan, fenfluramine, lithium, buspirone, or pindolol. Addition of tryptophan, the amino acid precursor of serotonin, has been reported helpful in an OCD patient taking clomipramine,[86] but ineffective in OCD patients taking trazodone.[87] At present, oral tryptophan supplements are not available in the United States because of evidence linking these preparations to the eosinophilia-myalgia syndrome, a serious and potentially fatal hematologic/connective tissue illness.[88] As discussed later in this section, a research group in Canada (where tryptophan is still available) reports that tryptophan, pindolol, and an SSRI, when given together, may yield positive results in patients with treatment-refractory OCD.[88]

In an open-label study, Hollander et al.[89] reported that the addition of the serotonin releaser and reuptake blocker *d,l*-fenfluramine to ongoing treatment with various SRIs led to improvement in OCD symptoms in six of seven patients. Subsequently, Judd et al.[90] reported that two clomipramine-treated OCD patients improved after addition of dexfenfluramine, which was recently released for the management of obesity. The use of dexfenfluramine as an adjunct to fluvoxamine cannot be recommended in the absence of controlled trials designed to assess efficacy and safety.

Early encouraging findings with lithium augmentation in OCD were not confirmed in subsequent double-blind, placebo-controlled trials.[91,92] No significant improvement in OC symptoms was observed after 4 weeks of double-blind lithium augmentation of ongoing clomipramine treatment in 16 OCD patients who had demonstrated a partial response to clomipramine.[91] Similarly, on the basis of stringent treatment response criteria, only 3 (15%) of 20 and 0 (0%) of 10 fluvoxamine-refractory patients with OCD responded, respectively, to 2- and 4-week trials of lithium addition to ongoing fluvoxamine treatment.[92] Thus, the efficacy of lithium addition in patients with OCD does not appear to approach the rate or quality of response to this treatment strategy typically seen in patients with treatment-resistant depression. However, in both studies, there was some improvement in depression ratings with addition of lithium. While the overall response rate is low, individual OCD patients, particularly those with prominent depressive symptoms, may benefit from lithium augmentation.

As was the case with lithium augmentation, initially encouraging findings with the serotonin (5-hydroxytryptamine; 5-HT) type 1A agonist buspirone have not been corroborated by subsequent double-blind trials.[93–95] For example, using a parallel-groups design, McDougle et al.[93] reported that buspirone added to the treatment of 33 patients with OCD who were refractory to fluvoxamine was no better than placebo in reducing OC, depressive, or anxiety symptoms. In this study, either buspirone (up to a maximal daily dose of 60 mg) or placebo was combined with fluvoxamine for 6 weeks in patients already taking fluvoxamine for 8 weeks. Together, these controlled studies suggest that addition of buspirone to SRI therapy is not an effective treatment strategy for most patients with OCD.

Studies in laboratory animals suggest that antidepressant-induced enhancement of serotonin neurotransmission does not occur immediately because of serotonin autoreceptor-mediated inhibition of firing rate and release. As these autoreceptors desensitize during chronic antidepressant administration, both firing rate and release recover, leading to a net increase in serotonin neurotransmission. A research group from Spain[96] hypothesized that addition of an agent that blocks somatodendritic 5-HT_{1A} autoreceptors, such as pindolol, might accelerate or augment the action of antidepressants in humans. Pindolol is a nonselective β-adrenergic antagonist that binds with high affinity to the 5-HT_{1A} receptor[97] and antagonizes the actions of 5-HT_{1A} agonists in animals[98] and humans.[99,100] Artigas et al. conducted an open-label study on the effects of pindolol augmentation of SRIs or monoamine oxidase inhibitors in patients with major depression and had encouraging results.[96] Blier and colleagues[101] at McGill have since examined the use of pindolol in OCD. They added pindolol (2.5 mg t.i.d.) to ongoing SRI treatment of nine patients with OCD who had not responded to SRIs alone.[101] Four weeks of combined pindolol-SRI treatment had a clear antidepressant effect in patients with depressive symptomatology but did not reduce severity of OC symptoms as reflected on the Y-BOCS. It is noteworthy, however, that addition of tryptophan to the SRI-pindolol regimen in 13 patients produced significant improvement in OC symptoms after 4 weeks, with additional gains after 6 weeks.[101] Blier et al. are conducting a controlled trial to confirm these exciting preliminary findings.

Clinicians often comedicate their SRI-resistant OCD patients with clomipramine and an SSRI even though there is little empirical support for the practice. One reason for adding a better tolerated SSRI has been the emergence of dose-limiting clomipramine-related side effects. In this vein, there are some encouraging case reports of coadministering fluoxetine and clomipramine in adolescents[102] and adults[77] with OCD. Another rationale for the combination is to use the SSRI to inhibit the degradation of clomipramine to its less serotonergic metabolites.[21] Several early studies in OCD patients treated with clomipramine found that response was correlated with plasma levels of the parent compound, but not its metabolite desmethylclomipramine.[103] In a recent study,[104] 21 patients with either depression or OCD were given combined fluvoxamine-clomipramine treatment. Most of the patients were said to have enjoyed a good response to the combination. Concomitant fluvoxamine was associated with elevations in plasma concentrations of clomipramine while the corresponding levels of the metabolites were lowered. No serious adverse events were observed despite CMI levels ranging as high as 500 to 1200 ng/mL in half the patients. Because of the risks associated with SRI-induced elevations in plasma levels of tricyclics, caution should be exercised when these drugs are used concurrently.[105] The potential for clomipramine to lower seizure threshold is of particular concern, making it advisable to measure plasma clomipramine levels before and after addition of an SSRI. In light of the limited options available and the widespread use of this approach, rigorous investigation of clomipramine-SSRI combinations in treatment-refractory OCD seems justified.

Conventional neuroleptics alone do not appear effective in OCD,[106] but there is evidence that conjoint SRI-

neuroleptic treatment may be beneficial in some cases of OCD.[107] To date, the putative subgroup that has received the most attention has been OCD with a comorbid chronic tic disorder. This research has been based on the phenomenologic, family/genetic, neurochemical, and neuroanatomic overlap between OCD and TS and the extensive preclinical literature documenting anatomic and functional interactions between the serotonin and dopamine systems in the brain.[106,108–111] Tourette's syndrome is a chronic neuropsychiatric disorder of childhood onset that is characterized by multiple motor and phonic tics that wax and wane in severity and by an array of behavioral problems, including symptoms of attention deficit hyperactivity disorder and OCD. Conventional neuroleptics, such as haloperidol and pimozide, have been the mainstay of treatment for TS.[108]

Riddle et al.[112] reported on the anti-OC benefits of adding an SRI to neuroleptic in two cases of concomitant TS and OCD. Subsequently, Delgado et al.[113] reported on a young man with coexisting TS and OCD who showed marked improvement in his OC symptoms as well as tics when pimozide was added to fluvoxamine. Of interest, OC symptoms returned and tics remained suppressed when fluvoxamine was discontinued and the patient was left on pimozide alone. This suggested that adequate control of his OC symptoms required coadministration of an SRI and a dopamine antagonist, whereas tics could be managed with a dopamine antagonist alone. This case was followed up with a successful open case series in which a low-dose neuroleptic (haloperidol or pimozide) was added to ongoing treatment in 17 nonpsychotic OCD patients unresponsive to fluvoxamine alone.[114] Findings from an independent retrospective review of five adolescents with TS and comorbid OC[115] are consistent with the results of the Yale group.

Results from a double-blind, placebo-controlled study of haloperidol addition to fluvoxamine-refractory patients with OCD lend further support to the efficacy of this combination treatment strategy.[107] Sixty-two patients received single-blind placebo treatment for 1 week, followed by 8 weeks of single-blind treatment with fluvoxamine. Thirty-four of these had an unsatisfactory response to 8 weeks of fluvoxamine monotherapy and were then randomly assigned (double-blind) to either 4 weeks of haloperidol (N = 17) or placebo (N = 17) in addition to a fixed daily dosage of fluvoxamine. A comorbid diagnosis of chronic tics or TS was present in 8 of the haloperidol group and 7 of the placebo group. Mean daily dose of haloperidol at the end of the 4-week trial was 6.2 ± 3.0 mg. Benztropine 0.5 mg b.i.d. was administered prophylactically to both the haloperidol and placebo groups. For the purpose of the ratings, tics were distinguished from tic-like compulsions (e.g., compulsive touching or blinking) on the basis of whether the patient attached a purpose or meaning to the behavior. For example, if a patient felt an urge to repeatedly touch an object, this would be rated as a compulsion only if it was preceded by a need to neutralize an obsessive thought or image; otherwise it would be labeled a complex motor tic.

The fluvoxamine-haloperidol combination was significantly superior to the fluvoxamine-placebo combination on the basis of both stringent categorical response criteria and mean change in weekly Y-BOCS scores. Eleven (65%) of 17 of the patients who received haloperidol were responders, whereas none of the placebo-treated group showed a response. In responders to addition of haloperidol, Y-BOCS scores decreased significantly from 25.1 ± 6.0 to 15.5 ± 9.1 or 39%. As predicted, most of the benefit of haloperidol addition to fluvoxamine occurred in the OCD patients with a chronic tic disorder. In those patients with a comorbid chronic tic disorder, Y-BOCS scores decreased from 25.5 ± 4.7 to 13.6 ± 8.0 (47%) after haloperidol addition. Eight (100%) of 8 patients with a current comorbid tic disorder were responders to haloperidol addition, whereas 3 (33%) of 9 patients without a tic disorder were responders. There were no significant differences in plasma fluvoxamine levels between the fluvoxamine-haloperidol and fluvoxamine-placebo groups at the end of the 4-week trial. Thus, it seems unlikely that the therapeutic action of haloperidol addition was mediated through pharmacokinetic effects.

In another SRI-neuroleptic combination trial, George et al.[116] found that a fluvoxamine and sulpiride (a dopamine-2 antagonist available in the United Kingdom) combination had synergistic effects in the treatment of both OC and tic symptoms. Fluvoxamine, when given by itself, exerted modest benefit in the control of OC and tic symptoms.[116] This somewhat favorable experience with fluvoxamine monotherapy for tics contrasts with scattered reports that SRIs may exacerbate[113] or even induce tics.[80] It is the clinical impression of one of the authors (W.K.G.) that the effect of fluvoxamine on tics is indeed variable, but that many patients experience some subjective improvement in tic severity that is difficult to confirm with direct observation.

Several brief reports suggest that risperidone, one of a newer generation of antipsychotics with a superior tolerability/safety profile, might alleviate OC symptoms when added to ongoing SRI therapy. In a study at Yale,[117] one of three TS children with comorbid OCD showed substantial improvement in OC symptoms when risperidone was added to paroxetine. McDougle et al.,[118] also of Yale, reported that three of three patients with primary OCD who were unresponsive to fluvoxamine alone showed marked improvement after risperidone was added to fluvoxamine.

FLUVOXAMINE IN OC-SPECTRUM DISORDERS

Some neuropsychiatric conditions have been referred to as OC-spectrum disorders primarily on the basis of their

similarities to OCD vis-à-vis characteristic clinical features (i.e., recurrent distressing thoughts or irresistible behaviors) and response to SRIs. Frequent comorbidity with OCD (e.g., Tourette's syndrome or autism) is another reason for the label of an OC-spectrum disorder. While major depression is the most frequently encountered comorbid major psychiatric disorder (and its morbid preoccupations have been likened to obsessions), it is not thought of as belonging to the OC-spectrum because of its distinct clinical features, course, and treatment response. Furthermore, the development of depression is usually presumed secondary to having OC symptoms. Of the OC-spectrum disorders, TS is the only one to date for which a relationship with some forms of OCD is supported by family/genetic data.[110]

Although it is beyond the scope of this article to discuss the validity of the inclusion of a particular disorder among the OC-spectrum, several general caveats are worth noting. First, some authors[119,120] have conceptualized OC-spectrum disorders and OCD itself as falling along a continuum from pure obsessiveness at one end, to compulsivity and finally to impulsivity at the other end. This range of behavioral expression coincides with the degree to which actions are inhibited, highly planned, or disinhibited, respectively. Alternatively, a gradient between risk avoidant and risk seeking behavior has been used to understand the constitutional differences underlying the compulsive/impulsive dimension.[121] One problem with these schema is that the differentiation of compulsive from impulsive behavior can be problematic at the clinical level. In addition, the hypothesis that OC-spectrum cases fall along different points of the compulsive/impulsive continuum needs to explain how both compulsive and impulsive behavior can coexist in the same individuals. For example, some cases of comorbid OCD and TS display both compulsive (e.g., ritualized grooming) and impulsive (e.g., inappropriate touching) behaviors. Second, counting conditions as members of the OC-spectrum primarily because of favorable response to SRIs is liable to be overinclusive. OCD stands out among major psychiatric disorders not for its robust response to SRIs—in fact, its magnitude and rate of response is generally less than in depression and panic disorder—but for the relative lack of response to other types of antidepressants or anxiolytics.[50] The technique for establishing the preferential efficacy of SRIs is best exemplified in the series of comparative clomipramine/desipramine trials conducted by researchers at the NIMH[4,5] This pharmacologic dissection strategy was employed in several other disorders (e.g., trichotillomania,[122] nail-biting,[123] autism,[124] and paraphilias[125]) bearing some phenomenological resemblance to OCD. Thus, demonstration of SRI effectiveness coupled with desipramine ineffectiveness is much stronger evidence for an association with OCD than efficacy of SRIs alone. Even when a condition shows a preferential SRI response (in the absence of other investigations disclosing shared pathobiology), one is limited to inferences about the mechanisms common to treatment.[50] Aware of the pitfalls of extrapolating from parallels in treatment response alone, Swedo et al.[126] questioned the hypothesis that OCD and trichotillomania are mediated by shared brain pathways after functional neuroimaging studies revealed differences between the two disorders.

The aforementioned limitations of the OC-spectrum construct notwithstanding, the following conditions have been frequently classified as such: among the somatoform disorders, body dysmorphic disorder (BDD)[127] and hypochondriasis[128,129]; the eating disorders, anorexia nervosa,[130] bulimia nervosa, and binge-eating disorder[131]; the childhood-onset disorders, autism,[124] Tourette's syndrome (TS), and Prader-Willi syndrome[132,133]; the impulse control disorders, trichotillomania,[134,135] pathological gambling,[136] compulsive nail biting (onychophagia),[123] kleptomania,[137] and compulsive buying[138]; and the paraphilias.[125] Available publications on the use of fluvoxamine in the aforementioned conditions are briefly reviewed below. Unfortunately, there are few double-blind, placebo-controlled trials of fluvoxamine.

One of the OC-spectrum disorders to receive the most systematic inquiry is BDD.[127,139] There have been no controlled treatment studies of BDD, but several open-label case series suggest that SRIs are beneficial for many of these patients, even some with delusional ideation.[140,141] In a retrospective analysis of 50 patients with BDD, those treated with clomipramine, fluoxetine, or fluvoxamine seemed to do better than those treated with tricyclics.[142] The six patients treated with fluvoxamine for a mean of 19 months were all rated as much or very much improved.[141] Phillips and McElroy[140] conducted an open-label trial of fluvoxamine (up to 300 mg daily) in 20 patients with BDD. Based on stringent outcome criteria, 14 (70%) of 20 were responders.[140] The authors note that "delusional patients were as likely to respond as nondelusional subjects, and insight significantly improved." Compared with BDD, there is much less published research on the possible relationship between hypochondriasis and OCD.[128,129] Currently, we are unaware of any published reports of fluvoxamine in hypochondriasis, although there are some positive reports of other SSRIs in this condition.[143]

The possible relationship between the eating disorders and OCD is receiving increased attention.[144–146] Jarry and Vaccarino,[147] in their review of neurochemical and phenomenological commonalities, suggest the occurrence of both eating disorders and OCD along a continuum. The preoccupations with body image and compulsive behaviors associated with dieting and eating (e.g., calorie counting or ritualized arrangement of food) in anorexia nervosa bear a strong phenomenological resemblance to the obsessions and compulsions of OCD. (It could be argued, however, that the relatively fixed idea of being overweight in

anorexia nervosa is more akin to the distorted bodily preoccupations seen in BDD than the good insight characteristic of OCD.) Frequent comorbidity and other lines of evidence also point to a more fundamental relationship between anorexia nervosa and OCD.[144,146] The compulsive drive behind bingeing, as well as the distressful thoughts that accompany unwanted weight gain, have led to consideration of bulimia nervosa and binge-eating disorder as related to OCD. Binge-eating disorder appears to be related to bulimia nervosa but does not involve behaviors to prevent weight gain such as purging or laxative use and is currently stated as an example of eating disorder not otherwise specified (NOS) in DSM-IV.[131] To our knowledge, there have been no reported cases of fluvoxamine treatment in anorexia nervosa, but both bulimia nervosa[148,149] and binge-eating disorder[150,151] have shown positive results with this medication. It should be noted that fluoxetine has been shown efficacious in the treatment of bulimia nervosa and has received a Food and Drug Administration (FDA) indication for this disorder.[152] An 8-week open trial of 10 patients with recurrent binge-eating who did not engage in self-induced vomiting showed a significant reduction in the frequency of binge-eating while treated with fluvoxamine 200 mg/day.[150] Hudson et al.[151] conducted a placebo-controlled study of fluvoxamine in 67 patients diagnosed with binge-eating disorder by DSM-IV criteria and also found a significant reduction in the frequency of binge-eating episodes as well as significant overall improvement. Studies of fluvoxamine in the prevention of relapse in bulimia nervosa have met with mixed results.[153–155]

Several of the disorders first diagnosed in childhood have been adopted as members of the OC-spectrum mostly on the basis of comorbid OCD or OC symptoms. The treatment of tic-related OCD with fluvoxamine was discussed earlier in this article. Autistic patients may exhibit classic compulsive symptoms such as repeating routine activities, ordering, hoarding, incessant questioning, touching, tapping, as well as other stereotyped behaviors.[156] In double-blind trials of autistic subjects, Gorden et al.[124] found that clomipramine was superior to desipramine and placebo in controlling autistic symptoms, anger, and compulsive, ritualized behaviors. McDougle et al.[157] described a 30-year-old man with coincident OCD and autism who experienced sustained clinical improvement in global outlook as well as OC symptoms while taking fluvoxamine 150 mg q.d. Harvey and Cooray[158] presented a case report of a 20-year-old autistic woman who displayed excessive and ritualized cleaning of the telephone, ritualized sniffing and smelling of objects, and repetitive ordering and arranging of objects and books in addition to repetitive stereotypic behavior. The patient was treated with fluvoxamine 100 mg/day and showed improvement in multiple areas at 6 weeks including behavior, language, and recovery of functional abilities supported by a substantial decline in Y-BOCS scores.[158]

Among the impulse control disorders, trichotillomania has been examined most closely with respect to its relationship with OCD.[159] Some authors have posited that pathologic grooming is the common thread between trichotillomania, onychophagia, and some forms of OCD.[135] While early reports of trichotillomania emphasized its co-occurrence with OCD and favorable response to SRIs,[122] later studies indicate that trichotillomania often exists in isolation[134] and that pharmacotherapy often fails.[159] While there are successful double-blind, controlled trials with clomipramine,[122] SSRI efficacy in trichotillomania has not been supported by most controlled trials of fluoxetine.[160,161] Recently, Christenson and Crow[159] completed an 8-week open trial of fluvoxamine (up to 300 mg/day) in 19 patients with trichotillomania. Subjects improved on four of five outcome measures, with the reduction from baseline ranging from 22% to 43%. However, only 4 (21%) of 19 subjects qualified as responders on the basis of stringent criteria, and a loss in efficacy appeared by the end of 6 months. Double-blind, placebo-controlled trials are needed to confirm the efficacy of fluvoxamine in the acute and long-term treatment of trichotillomania.

Another impulse control disorder sometimes considered within the OC-spectrum is pathological gambling, an underdiagnosed problem with deleterious consequences.[136] OC-like behaviors in this disorder include difficulty resisting thoughts and urges to perform repetitive behavior, an increased sense of tension prior to performing the behavior, and a subsequent sense of relief after completing it. Literature on pharmacologic treatment of this illness is scant, but some effectiveness has been attributed to clomipramine use.[162] Wong and Hollander[163] have reported positive preliminary results in six patients with pathological gambling and a positive family history of pathological gambling who were treated with fluvoxamine for 8 weeks. Four of six were responders as defined by "much" or "very much improved" on the CGI and a ≥ 25% decrease in scores on the Y-BOCS adapted for pathological gambling.

Compulsive buying is characterized by an uncontrollable and senseless urge by the person to buy.[138,164] Its nosologic status is unclear, but some have classified it as an impulse control disorder NOS in DSM-IV. Black[165] described a case report of a 35-year-old woman who spent much of her life compulsively shopping, although she acknowledged that it was excessive and caused financial difficulties. The patient was treated with fluvoxamine 150 mg/day and after 8 weeks reported decreased thoughts about shopping and less time actually shopping. Black[138] later performed an open-label study of fluvoxamine in 10 patients with moderate to severe compulsive buying. By Week 5 of a 9-week trial, 9 of 10 responded as defined by a 50% improvement on the Y-BOCS adapted for shopping.

Travin[166] attempts to explain the often confusing diagnostic terminology and categorization of compulsive sexual behaviors. One framework for understanding this group of paraphilic and nonparaphilic disorders is through an obsessive-compulsive spectrum disorder model where the behavior is motivated by anxiety reduction as opposed to desire. Kruesi et al.[125] studied 15 paraphiliacs in a double-blind, crossover study of clomipramine versus desipramine. Although the study is limited by a small sample size (only 8 completers), unlike OCD, there was no preferential benefit of clomipramine over desipramine. Kruesi et al. acknowledge that the heterogeneity of the paraphilias included in the study may have affected the results. Stein et al.[167] described an unsuccessful 8-week trial of fluvoxamine in one patient with a paraphilia who experienced decreased masturbation secondary to impotence and a delay in ejaculation without a change in fantasies. In contrast, Zohar et al.[168] successfully treated a male exhibitionist who had compulsive masturbation by using fluvoxamine up to 300 mg/day. There was a complete resolution of symptoms after 2 weeks of fluvoxamine treatment whereas desipramine induced a relapse in the same individual.

RECOMMENDATIONS ON THE USE OF FLUVOXAMINE IN OCD

Dosing

The usual adult dose of fluvoxamine is between 100 mg and 300 mg daily. It is unusual to find patients with OCD who respond to doses less than 100 mg daily. A starting dose not exceeding 50 mg taken after an evening meal may help minimize nausea and other early side effects that might lead to premature termination of treatment. In some cases, a starting dose of 25 mg may be warranted. In the early stages of treatment, the primary objective is to promote compliance. Although patients may be experiencing marked distress and functional impairment, most have had symptoms for years before presenting for treatment. The dose of fluvoxamine can be increased by 50-mg increments every 3 to 4 days in outpatients (even faster in inpatients), but this dose escalation should be reduced to 50 mg every week if the patient is troubled by side effects.

There are no fixed-dose trials of fluvoxamine to guide our selection of the optimal therapeutic dose. However, based on clinical experience, we recommend an initial target dose of 200 mg daily. If the patient is not showing significant improvement after 8 weeks at this dose—and provided he/she is tolerating it—the dose should be increased to 300 mg daily for at least 4 weeks before abandoning the trial as unsuccessful. It is the clinical impression of one of the authors (W.K.G.) that, compared with fluvoxamine, fluoxetine tends to induce more activation; conversely, fluvoxamine is generally more sedating. For these reasons, we generally administer fluoxetine in the morning, whereas the bulk of the fluvoxamine dose is usually given at bedtime. If the patient reports disrupted sleep, then the dosage timing should be reversed such that the bulk of fluvoxamine is taken in the morning. The dosage of fluvoxamine should be reduced in patients with evidence of hepatic dysfunction. In the elderly, the dose should be increased more slowly and the maximum daily dose may be lower.

Based on the multicenter trial of fluvoxamine in children and adolescents with OCD,[78] it is advisable to start patients in this age range on fluvoxamine 25 mg at bedtime. This dose should be continued for approximately 3 days and then increased by 25-mg increments every 3 to 4 days until a maximum daily dose of 200 mg is achieved. Fluvoxamine should be given twice daily for daily doses of 75 mg or greater with the larger dose given at bedtime.

Adverse events have been associated with abrupt discontinuation of the SSRIs paroxetine,[169–176] fluvoxamine,[177–179] and sertraline.[170–181] Relatively fewer such reports after abrupt cessation of fluoxetine[182–184] may reflect the long half-lives of the drug and its metabolite norfluoxetine.[169,170] The constellation of symptoms reported is somewhat variable, but has most frequently included flulike symptoms, vertigo/dizziness, insomnia, vivid dreams, irritability, and headaches lasting from several days to more than a week. No medically significant events have been documented, but patients often describe marked discomfort. To reduce the risk of a discontinuation syndrome, a gradual taper of fluvoxamine is generally recommended in patients who have received chronic treatment with more than 100 mg daily.

Management of Side Effects

In general, fluvoxamine is well-tolerated, yet, when side effects do occur, their appropriate management can reduce discomfort, improve quality of life, and thereby foster compliance. Literature on the management of fluvoxamine-induced side effects is limited to case reports and generally follows clinical experience gained with other SSRIs. Since side effects are often dose related, dosage reduction is always the first consideration. However, the addition of a second medication may be indicated to counteract the side effects of nausea, insomnia, or sexual dysfunction.

Gastrointestinal side effects are often reduced by taking fluvoxamine with food, which, as noted earlier, does not affect the absorption of the drug. As with the other SSRIs, nausea frequently occurs early in the course of treatment and dissipates over time, only infrequently leading to drug discontinuation. If nausea develops, upward titration should be suspended until this side effect begins to abate. However, in patients with persistent nausea, adjunctive medication may be considered. There has been one positive open label study of the gastric promotility agent cisapride (5 mg b.i.d.) in eight patients

with SSRI (fluoxetine, paroxetine, and sertraline)-induced nausea.[185] To the extent that this effect of cisapride is mediated through its serotonin receptor type 3 (5-HT_3) blocking action,[186] other 5-HT_3 antagonists such as ondansetron may also prove beneficial.[187] There is currently no published literature regarding an interaction between cisapride and fluvoxamine. However, combining cisapride with agents that inhibit cytochrome P450 3A4 isoenzyme, such as erythromycin, has resulted in life-threatening cardiac arrhythmias[188]; therefore, conjoint use of cisapride and fluvoxamine should be avoided.

In evaluating insomnia in a patient receiving fluvoxamine, it is important to rule out insomnia secondary to an inadequately treated comorbid depression or persistent obsessional thoughts. Once this is done, the clinician is often faced with choosing a medication for symptomatic treatment of this side effect. The triazolopyridine antidepressant trazodone has been a popular choice because of its sedative effects in low doses. There has been one double-blind, placebo-controlled study of trazodone (50–100 mg) for antidepressant-associated insomnia in 17 depressed patients.[189] Thirteen patients receiving fluoxetine and 2 patients receiving bupropion completed the study. One patient dropped out of the study secondary to excessive daytime sedation, and 1 dropped out after no response with placebo. Of the completers, 67% experienced improvement with trazodone and 13% with placebo. It has not been determined if trazodone addition has an effect (positive or negative) on OC symptoms. In the only double-blind, placebo-controlled trial, trazodone monotherapy failed to demonstrate significant anti-OC efficacy.[190] This may be a moot point, as the dose of trazodone that is used for sleep induction is considerably lower than that used for treating depression. Clinical practice would indicate that an alternative to trazodone for drug-induced insomnia may be a trial of a hypnotic dose of a benzodiazepine. There are no published reports addressing this specific use of the benzodiazepines. However, in choosing an agent for use in combination with fluvoxamine, benzodiazepines metabolized via cytochrome P450 3A4 isoenzyme (alprazolam, triazolam, diazepam) should generally be avoided or used in lower doses to avoid benzodiazepine toxicity. Preferred agents may be the 3-hydroxybenzodiazepines (lorazepam, oxazepam, temazepam) that are primarily metabolized through glucuronidation.

Sexual dysfunction in patients receiving psychotropic medications is best approached through a systematic evaluation to determine causality.[191] For cases in which the SRI seems responsible, the literature offers several different approaches to consider. Cyproheptadine is an antihistamine and 5-HT_2 antagonist that has been reported to reverse anorgasmia and ejaculatory delay secondary to serotonergic medications such as fluoxetine.[192,193] There has been one case report of successful treatment of fluvoxamine-induced anorgasmia in a 63-year-old man using cyproheptadine 4 to 6 mg 2 hours prior to intercourse.[194] Sedation is common with cyproheptadine and may present a dose-limiting side effect. Additionally, there has been concern about the capacity of cyproheptadine to reverse the antidepressant effects of fluoxetine.[195] In an open trial,[196] the α_2-antagonist yohimbine was reported to counter the sexual side effects of clomipramine and fluoxetine in six patients. The authors note that dosing had to be individualized across a broad range (2.7–16.2 mg, given on a p.r.n. basis, 2–4 hours before intercourse) in order to achieve benefit and avoid side effects of shakiness, fatigue, excessive sweating, anxiety, and insomnia. Yohimbine was given on a regular dosing schedule (5.4 mg t.i.d.) in another open trial[197] to nine patients receiving 20 to 40 mg of fluoxetine. Eight of the nine patients reported improvement in sexual functioning. Five patients reported side effects of nausea, anxiety, insomnia, and urinary frequency, which led to discontinuation of yohimbine in two cases. A third agent, amantadine (100–200 mg/day), has been used to counter fluoxetine-induced anorgasmia in a seven-patient case series.[198] Anorgasmia resolved in five of the patients, but persisted in two. There were no adverse effects reported in this series. There has been one case report of fluoxetine-induced sexual side effects resolving in a 50-year-old man after the addition of bupropion.[199] The mechanism by which bupropion resolved this sexual dysfunction is unknown, but the authors suggest that it may be related to its dopamine reuptake inhibiting actions. The benefit of a drug holiday has been evaluated in an open trial of 30 patients experiencing SSRI-induced sexual dysfunction.[200] Patients receiving paroxetine and sertraline, but not fluoxetine, reported significant improvement in sexual functioning after a 2-day drug holiday. There were no statistically significant increases in depression ratings following discontinuation of the antidepressant. The comparable half-life of fluvoxamine would support a trial of similar brief drug holidays for countering sexual side effects.

SUMMARY

In summary, the mainstay of pharmacologic treatment for OCD is an adequate trial with a potent SRI. The potent SRIs clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline have been shown in double-blind trials to be significantly better than placebo in the treatment of OCD. While these medications rarely eliminate all symptoms of OCD, they represent a major advance over previously available biological treatments. A trial with a potent SRI in OCD should not be abandoned as a failure until the end of Week 12 unless intolerable side effects emerge.

Fluvoxamine, the subject of this review, is an effective and generally well-tolerated treatment for OCD and has an extensive clinical database supporting its safety. The most common side effects are those typical of SSRIs as a class:

nausea, insomnia, somnolence, and sexual dysfunction. Some evidence suggests that the incidence of sexual dysfunction may be somewhat lower with fluvoxamine compared with other SSRIs. Compared with fluoxetine, fluvoxamine may induce less activation, but more drowsiness. The effective dose range is between 100 and 300 mg daily and can usually be given as a single nighttime dose. Preliminary evidence supports the effectiveness of fluvoxamine in children and adolescents with OCD. Recent double-blind comparative trials suggest that fluvoxamine and clomipramine possess equivalent efficacy in OCD.

A growing appreciation of the cytochrome P450 enzyme systems has led to increased scrutiny of potential drug-drug interactions. Some of the nonsedating antihistamines (i.e., terfenadine and astemizole) should not be used in combination with fluvoxamine, sertraline, fluoxetine, or nefazodone because of the potential risk of cardiotoxicity. By the same token, the gastric prokinetic agent cisapride should not be prescribed along with fluvoxamine. It appears that another antihistamine, loratadine, can be used safely with fluvoxamine. The pharmacokinetic profiles of cetirizine and fexofenadine, two newer antihistamines, suggest that fluvoxamine should not interfere with their biotransformation. As with other SRIs, MAOIs and fluvoxamine should not be prescribed within 2 to 3 weeks of each other. Concomitant administration of the following medications with fluvoxamine requires careful monitoring for clinical and/or laboratory signs of toxicity: warfarin, theophylline, propranolol, clozapine, phenytoin, carbamazepine, alprazolam, some tricyclics, and methadone. For most of these drugs, the dose should be reduced (e.g., by 50% in the case of alprazolam) when given with fluvoxamine. Coadministration of diazepam should be avoided because fluvoxamine reduces the clearance of both diazepam and its active metabolite desmethyldiazepam, which may lead to accumulation of both species during chronic administration. Metabolism of lorazepam, oxazepam, or temazepam should not be affected by fluvoxamine. Although the package insert warns against concomitant use of dextrofenfluramine and SRIs, the preclinical and clinical basis for this concern is ill-defined.

Fluvoxamine has shown promise in the treatment of several so-called OC-spectrum disorders, including binge-eating disorder, BDD, trichotillomania, compulsive buying, and pathological gambling. Some features of autism also seem to improve with fluvoxamine. Additional double-blind, placebo-controlled studies are needed to establish the efficacy of fluvoxamine in these conditions. A combination of fluvoxamine and the neuroleptic haloperidol was effective in a subgroup of fluvoxamine-refractory patients with comorbid OCD and chronic tics. The common clinical practice of combining clomipramine with SSRIs, such as fluvoxamine, needs to be subjected to rigorous efficacy and safety assessment. Future studies are needed to determine if behavior therapy can reduce the high relapse rate that often occurs after SRI discontinuation in OCD.

Drug names: alprazolam (Xanax), amantadine (Symmetrel), astemizole (Hismanal), benztropine (Cogentin and others), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), cetirizine (Zyrtec), chloral hydrate (Noctec), cisapride (Propulsid), clomipramine (Anafranil), clozapine (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), erythromycin (E-Mycin and others), fenfluramine (Pondimin), fexofenadine (Allegra), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), imipramine (Tofranil and others), ketoconazole (Nizoral), loratadine (Claritin), lorazepam (Ativan and others), methadone (Methadose and others), nefazodone (Serzone), ondansetron (Zofran), oxazepam (Serax and others), paroxetine (Paxil), phenytoin (Dilantin and others), pimozide (Orap), pindolol (Visken), propranolol (Inderal and others), risperidone (Risperdal), sertraline (Zoloft), sulpiride (Dogmatyl), temazepam (Restoril and others), terfenadine (Seldane), theophylline (Constant-T and others), trazodone (Desyrel and others), triazolam (Halcion), warfarin (Coumadin and others), yohimbine (Yocon and others).

REFERENCES

1. Renynghe de Voxrie GV. Anafranil (G 34586) in obsessive neurosis. Acta Neurol Belg 1968;68:787–792
2. Yaryura-Tobias JA, Neziroglu F, Bergman L. Chlorimipramine, for obsession-compulsive neurosis: an organic approach. Current Therapeutic Research 1976;20:541–548
3. The Clomipramine Collaborative Study Group. Clomipramine in the treatment of patients with obsessive-compulsive disorder. Arch Gen Psychiatry 1991;48:730–738
4. Zohar J, Insel TR. Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment and pathophysiology. Biol Psychiatry 1987;22:667–687
5. Leonard H, Swedo S, Coffey M, et al. Clomipramine vs desipramine in childhood obsessive-compulsive disorder. Psychopharmacol Bull 1988; 24:43–45
6. Rasmussen SA, Goodman WK, Greist JH, et al. Fluvoxamine in the treatment of obsessive-compulsive disorder: a multi-center double-blind placebo-controlled study in outpatients. Am J Psychiatry. In press
7. Tollefson GD, Rampey AH Jr, Potvin JR, et al. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 1994;51:559–567
8. Wheadon DE, Bushell WD, Steiner M. A fixed dose comparison of 20, 40, or 60 mg paroxetine to placebo in the treatment of obsessive-compulsive disorder. Abstracts of Panels and Posters of the 32nd Annual Meeting of the American College of Neuropsychopharmacology; December 13–17, 1993; Honolulu, Hawaii
9. Chouinard G, Goodman W, Greist J, et al. Obsessive-compulsive disorder—treatment with sertraline: a multicenter study. Psychopharmacol Bull 1990;26:279–284
10. Jefferson JE, Greist JH. The pharmacotherapy of obsessive-compulsive disorder. Psychiatric Annals 1996;26(4):202–209
11. Palmer KJ, Benfield P. Fluvoxamine: an overview of its pharmacological properties and review of its therapeutic potential in non-depressive disorders. CNS Drugs 1994;1(1):57–87
12. Abramowicz M, ed. Fluvoxamine for obsessive-compulsive disorder. Med Lett Drugs Ther 1995;37(942):13–14
13. deVries MH, Raghoebar M, Mathlener IS, et al. Single and multiple oral dose fluvoxamine kinetics in young and elderly subjects. Ther Drug Monit 1992;14:493–498
14. Wright S, Dawling S, Ashford JJ. Excretion of fluvoxamine in breast milk. Br J Clin Pharmacol 1991;31:209
15. Buist A, Norman TR, Dennerstein L. Breast-feeding and the use of psychotropic medication: a review. J Affect Disord 1990;19:197–206
16. Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. Am J Psychiatry 1996;153(3):311–320
17. Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. Eur J Clin Pharmacol 1994;46:35–39

18. DeVane CL. Comparative safety and tolerability of selective serotonin reuptake inhibitors. Human Psychopharmacology 1995;10:S185–S193
19. DeQuardo JR, Roberts M. Elevated clozapine levels after fluvoxamine initiation. Am J Psychiatry 1996;153:840–841
20. Spina E, Campo GM, Avenoso A, et al. Interaction between fluvoxamine and imipramine/desipramine in four patients. Ther Drug Monit 1992;14: 194–196
21. Hartter S, Arand M, Oesch F, et al. Non-competitive inhibition of clomipramine *N*-demethylation of fluvoxamine. Psychopharmacology 1995;117: 149–153
22. Honig PK, Wortham DC, Zamani K, et al. Terfenadine-ketoconazole interaction. JAMA 1993;269:1513–1518
23. Von Moltke LL, Greenblatt DJ, Duan SX, et al. Inhibition of terfenadine metabolism in vitro by azole antifungal agents and by selective serotonin reuptake inhibitor antidepressants: relation to pharmacokinetic interactions in vivo. J Clin Psychopharmacol 1966;16:104–112
24. Claritin (loratadine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1997:2349–2350
25. Sale ME, Barbey JT, Woosley RL, et al. The electrocardiographic effects of cetirizine in normal subjects. Clin Pharmacol Ther 1994;56:295–301
26. Hoeschst Marion Roussel Data on file; Drug Topics Red Book Update, October 1996
27. Harmant J, van Rijckevorsel-Harmant K, de Barsy T, et al. Fluvoxamine: an antidepressant with low (or no) epileptogenic effect. Lancet 1990; 336:386
28. Trabert W, Hohagen F, Winkelman G, et al. A seizure, and electroencephalographic signs of a lowered seizure threshold, associated with fluvoxamine treatment of obsessive-compulsive disorder. Pharmacopsychiatry 1995;28(3):95–97
29. Hansten PD, Horn RJ, eds. Drug Interactions and Updates. Vancouver, Wash: Applied Therapeutics, Inc; 1996
30. Hendricks B, Floris M. A controlled pilot-study of the combination of fluvoxamine and lithium. Current Therapeutic Research, Clinical & Experimental 1991;4:106–110
31. Ohman R, Spigset O. Serotonin syndrome induced by fluvoxamine-lithium interaction. Pharmacopsychiatry 1993;16:263
32. Delgado PF, Price LH, Charney DS, et al. Efficacy of fluvoxamine in treatment-refractory depression. J Affect Disord 1988;15:55–60
33. Lejoyeux M, Ades J, Rouillon F. Serotonin syndrome: incidence, symptoms and treatment. CNS Drugs 1994;2:132–143
34. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148:705–713
35. Finley PR, Warner MD, Peabody CA. Clinical relevance of drug interactions with lithium. Clin Pharmacokinet 1995;29:172–191
36. Garnier R, Azoyan P, Chataigner D, et al. Acute fluvoxamine poisoning. J Int Med Res 1993;21:197–208
37. Adverse Reaction Information System Database. 1996. Solvay Duphar, Marietta, Ga.
38. Lapierre YD, Browne M, Horn E, et al. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry 1987;48:65–68
39. Conti L, Dell'Osso L, Re F, et al. Fluvoxamine maleate: double-blind clinical trial vs placebo in hospitalised depressed patients. Current Therapeutic Research 1988;43(3):468–480
40. Feighner JP, Boyer WF, Meredith CH, et al. A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. Int Clin Psychopharmacol 1989;4:239–244
41. March JS, Kobak KA, Jefferson JW, et al. A double-blind, placebo-controlled trial of fluvoxamine versus imipramine in outpatients with major depression. J Clin Psychiatry 1990;51:200–202
42. Coleman BS, Block BA. Fluvoxamine maleate, a serotonergic antidepressant: in comparison with chlorimipramine. Prog Neuropsychopharmacol Biol Psychiatry 1982;6:475–478
43. de Wilde JE, Mertens C, Wakelin JS. Clinical trials of fluvoxamine vs chlorimipramine with single and three times daily dosing. Br J Clin Pharmacol 1982;15:427S–431S
44. Price LH, Goodman WK, Charney DS, et al. Treatment of severe obsessive-compulsive disorder with fluvoxamine. Am J Psychiatry 1987;144: 1059–1061
45. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
46. Perse TL, Greist JH, Jefferson JW, et al. Fluvoxamine treatment of obsessive-compulsive disorder. Am J Psychiatry 1988;144:1543–1548
47. Goodman WK, Price LH, Rasmussen SA, et al. The efficacy of fluvoxamine in obsessive compulsive disorder: a double-blind comparison with placebo. Arch Gen Psychiatry 1989;46:36–44
48. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry 1989;46:1006–1011
49. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, II: validity. Arch Gen Psychiatry 1989;46:1012–1016
50. Goodman WK, Price LH, Delgado PL, et al. Specificity of serotonin reuptake inhibitors in the treatment of obsessive compulsive disorder: comparison of fluvoxamine and desipramine. Arch Gen Psychiatry 1990;47: 577–585
51. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
52. Mavissakalian M, Turner SM, Michelson L, et al. Tricyclic antidepressants in obsessive-compulsive disorder: antiobsessional or antidepressant agents? II. Am J Psychiatry 1985;142:572–576
53. Marks IM, Stern RS, Mawson D, et al. Clomipramine and exposure for obsessive-compulsive rituals. Br J Psychiatry 1980;136:1–25
54. Insel TR, Murphy DI, Cohen RM, et al. Obsessive-compulsive disorder: a double blind trial of clomipramine and clorgyline. Arch Gen Psychiatry 1983;40:605–612
55. Ackerman DL, Greenland S, Bystritsky A, et al. Predictors of treatment response in obsessive-compulsive disorder: multivariate analyses from a multicenter trial of clomipramine. J Clin Psychopharmacol 1994;14:247–254
56. Jenike MA, Baer L, Minichiello WE, et al. Concomitant obsessive-compulsive disorder and schizotypal personality disorder. Am J Psychiatry 1986; 143:530–533
57. McDougle CJ, Goodman WK, Leckman JF, et al. The efficacy of fluvoxamine in obsessive compulsive disorder: effects of comorbid chronic tic disorder. J Clin Psychopharmacol 1993;13(5):354–358
58. Pigott TA, Pato MT, Bernstein SE, et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder: behavioral and biological results. Arch Gen Psychiatry 1990;47:926–932
59. Jenike MA, Baer L, Greist JH. Clomipramine versus fluoxetine in obsessive-compulsive disorder: a retrospective comparison of side effects and efficacy. J Clin Psychopharmacol 1990;10:122–124
60. Griest JH, Jefferson JW, Kozak KA, et al. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder: a meta-analysis. Arch Gen Psychiatry 1995;52:53–60
61. Wachter KW. Disturbed by meta-analysis? Science 1988;241:1407–1408
62. Koran LM, McElroy SL, Davidson JRT, et al. Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol 1996;16:121–129
63. Smeraldi E, Erzegovesi S, Bianchi I, et al. Fluvoxamine vs clomipramine treatment in obsessive-compulsive disorder: a preliminary study. New Trends in Experimental and Clinical Psychiatry 1992;7(2):63–65
64. Tamimi RR, Mavissakalian MR, Jones B, et al. Clomipramine versus fluvoxamine in obsessive-compulsive disorder. Ann Clin Psychiatry 1991;3: 275–279
65. Freeman CPL, Trimble MR, Deakin JFW, et al. Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. J Clin Psychiatry 1994;55:301–305
66. Mavissakalian MR, Jones B, Olson S. Absence of placebo response in obsessive-compulsive disorder. J Nerv Ment Dis 1990;178:268–270
67. Steiner M, Bushnell W, Gergel I, et al. Long-term treatment and prevention of relapse of OCD with paroxetine. In: New Research Program and Abstracts of the 148th Annual Meeting of the American Psychiatric Association; May 20–25, 1995; Miami, Fla. Abstract NR354:150
68. Ravizza L, Barzega G, Bellino S, et al. Drug treatment of obsessive-compulsive disorder (OCD): long-term trial with clomipramine and selective serotonin reuptake inhibitors. Psychopharmacol Bull 1996;32(1):167–173
69. Mallya GK, White K, Waternaux C, et al. Short- and long-term treatment of obsessive-compulsive disorder with fluvoxamine. Ann Clin Psychiatry 1992;4(2):77–80
70. Pato MT, Zohar-Kadouch R, Zohar J, et al. Return of symptoms after discontinuation of clomipramine in patients with obsessive compulsive disorder. Am J Psychiatry 1988;145:1521–1525
71. Leonard HL, Swedo SE, Lenane MC, et al. A double-blind desipramine substitution during long-term clomipramine treatment in children and adolescents with obsessive-compulsive disorder. Arch Gen Psychiatry 1991; 48:922–927

72. Pato MT, Hill JL, Murphy DL. A clomipramine dosage reduction in the course of long-term treatment of obsessive-compulsive disorder patients. Psychopharmacol Bull 1990;26:211–214
73. Back B, Uhde TW. Treatment of elective mutism with fluoxetine: a double-blind, placebo controlled study. J Am Acad Child Adolesc Psychiatry 1994; 33(7):1000–1006
74. Simeon JG, Dinicola VF, Ferguson HB, et al. Adolescent depression: a placebo controlled fluoxetine treatment study and follow-up. Prog Neuropsychopharmacol Biol Psychiatry 1990;14:791–795
75. Geller DA, Biederman J, Reed ED, et al. Similarities in response to fluoxetine in the treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 1995;34(1):36–44
76. Cook EH Jr, Rowlett R, Jaselskis C, et al. Fluoxetine treatment of children and adults with autistic disorder and mental retardation. J Am Acad Child Adolesc Psychiatry 1992;31:739–745
77. Apter A, Ratzoni G, King RA, et al. Fluvoxamine open-label treatment of adolescent inpatients with obsessive-compulsive disorder or depression. J Am Acad Child Adolesc Psychiatry 1994;33(3):342–348
78. Riddle MA, Claghorn J, Gaffney G, et al. A controlled trial of fluvoxamine for OCD in children and adolescents. Biol Psychiatry 1996;39(7):568
79. Diaferia G, Mundo E, Bianchi Y, et al. Behavioral side effects in obsessive-compulsive patients treated with fluvoxamine: a clinical description. J Clin Psychopharmacol 1994;14:78–79
80. Fennig S, Naisberg Fennig S, Pato M, et al. Emergence of Symptoms of Tourette's syndrome during fluvoxamine treatment of obsessive-compulsive disorder. British J Psychiatry 1994;164:839–841
81. Goodman WK, McDougle CJ, Byerly MJ, et al. New approaches to treatment-refractory obsessive compulsive disorder. In: Montgomery S, Halbreich U, eds. Pharmacotherapy of Mood and Cognition. In press
82. Greist JH. An integrated approach to treatment of obsessive compulsive disorder. J Clin Psychiatry 1992;53(4, suppl):38–41
83. Mattes JA. Fluvoxamine in obsessive-compulsive nonresponders to clomipramine or fluoxetine [letter]. Am J Psychiatry 1994;151:1524
84. Greist J, Chouinard G, DuBoff E, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 1995;52:289–295
85. Byerly WJ, Goodman WK, Christensen R. High doses of sertraline for treatment-resistant obsessive-compulsive disorder [letter]. Am J Psychiatry 1996;153:1232–1233
86. Rasmussen SA. Lithium and tryptophan augmentation in clomipramine resistant obsessive-compulsive disorder. Am J Psychiatry 1984;141: 1283–1285
87. Mattes JA. A pilot study of combined trazodone and tryptophan in obsessive-compulsive disorder. Int Clin Psychopharmacol 1986;1:170–173
88. Hertzman PA, Blevins WL, Mayer J, et al. Association of the eosinophilia-myalgia syndrome with the ingestion of tryptophan. N Eng J Med 1990; 322:869–873
89. Hollander E, DeCaria CM, Schneier FR, et al. Fenfluramine augmentation of serotonin reuptake blockade antiobsessional treatment. J Clin Psychiatry 1990;51:119–123
90. Judd FK, Chua P, Norman LC, et al. Fenfluramine augmentation of clomipramine treatment of obsessive compulsive disorder. Aust N Z J Psychiatry 1991;25:412–414
91. Pigott TA, Pato MT, L'Heureux F, et al. A controlled comparison of adjuvant lithium carbonate or thyroid hormone in clomipramine-treated patients with obsessive-compulsive disorder. J Clin Psychopharmacol 1991;11: 242–248
92. McDougle CJ, Price LH, Goodman WK, et al. A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. J Clin Psychopharmacol 1991;11:175–184
93. McDougle CJ, Goodman WK, Leckman JF, et al. Limited therapeutic effect of the addition of buspirone in fluvoxamine-refractory obsessive compulsive disorder. Am J Psychiatry 1993;150:647–649
94. Pigott TA, L'Heureux F, Hill JH, et al. A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated OCD patients. J Clin Psychopharmacol 1992;12:11–18
95. Grady TA, Pigott TA, L'Heureux F, et al. Double-blind study of adjuvant buspirone for fluoxetine-treated patients with obsessive-compulsive disorder. Am J Psychiatry 1993;150:819–821
96. Artigas F, Perez V, Alvarez E. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch Gen Psychiatry 1994;51:248–251
97. Hoyer D. Functional correlates of serotonin 5-HT1 recognition sites. Journal of Receptor Research 1988;8:59–81
98. Tricklebank M, Forler C, Fozard J. The involvement of subtypes of the 5-HT1 receptor and of catecholaminergic systems in the behavioral response to 8-hydroxy-2-(di-n-propylamino) tetralin in the rat. Eur J Pharmacol 1984;106:271–282
99. Coccaro E, Gabriel S, Siever L. Buspirone challenge: preliminary evidence for a role for central 5-HT1A receptor function in impulsive aggressive behavior in humans. Psychopharmacol Bull 1990;26:393–405
100. Anderson IM, Cowen PJ. Effect of pindolol on endocrine and temperature responses to buspirone in healthy volunteers. Psychopharmacology 1992;106:428–432
101. Blier P, Bergeron R. Sequential administration of augmentation strategies in treatment-resistant obsessive-compulsive disorder: preliminary findings. Int Clin Psychopharmacol 1966;11:37–44
102. Simeon JG, Thatte S, Wiggins D. Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. Psychopharmacol Bull 1990;26:285–290
103. Thoren P, Asberg M, Cronholm B, et al. Clomipramine treatment of obsessive-compulsive disorder, I: a controlled clinical trial. Arch Gen Psychiatry 1980;37:1281–1285
104. Szegedi A, Wetzel H, Leal M, et al. Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety, and tolerability data. J Clin Psychiatry 1996;57:257–264
105. Rosenstein DL, Takeshita J, Nelson JC. Fluoxetine-induced elevation and prolongation of tricyclic levels in overdose [letter]. Am J Psychiatry 1991;148:807
106. Goodman WK, McDougle CJ, Price LH, et al. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? J Clin Psychiatry 1990;51(8, suppl):36–43
107. McDougle CJ, Goodman WK, Leckman JF, et al. Haloperidol addition in fluvoxamine-refractory obsessive compulsive disorder: a double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry 1994;51:302–308
108. Leckman JF, Pauls DL, Cohen DJ. Tic disorders. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1665–1674
109. Holzer JC, Goodman WK, McDougle CJ, et al. Obsessive-compulsive disorder with and without a chronic tic disorder: a comparison of symptoms in 70 patients. Br J Psychiatry 1994;164:469–473
110. Pauls DL, Towbin KE, Leckman JF, et al. Gilles de la Tourette's syndrome and obsessive-compulsive disorder: evidence supporting a genetic relationship. Arch Gen Psychiatry 1986;43:1180–1182
111. Pauls DL, Alsobrook JP, Goodman WK, et al. A family study of obsessive compulsive disorder. Am J Psychiatry 1995;152:76–84
112. Riddle MA, Leckman JF, Hardin MT, et al. Fluoxetine treatment of obsessions and compulsions in patients with Tourette's syndrome. Am J Psychiatry 1988;145:1173–1174
113. Delgado PL, Goodman WK, Price LH, et al. Fluvoxamine/pimozide treatment of concurrent Tourette's and obsessive-compulsive disorder. Br J Psychiatry 1990;157:762–765
114. McDougle CJ, Goodman WK, Price LH, et al. Neuroleptic addition in fluvoxamine-refractory obsessive compulsive disorder: an open case series. Am J Psychiatry 1990;147:652–654
115. Hawkridge S, Stein DJ, Bouwer C. Combined pharmacotherapy for TS and OCD. J Am Acad Child Adolesc Psychiatry 1996;35(6):703
116. George MS, Trimble MR, Robertson MM. Fluvoxamine and sulpiride in comorbid obsessive-compulsive disorder and Gilles de la Tourette syndrome. Human Psychopharmacology 1993;8:327–334
117. Lombroso PJ, Scahill L, King RA, et al. Risperidone treatment of children and adolescents with chronic tic disorders: a preliminary report. J Am Acad Child Adoles Psychiatry 1995;34(9):1147–1152
118. McDougle CJ, Fleischmann RL, Epperson CN, et al. Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. J Clin Psychiatry 1995;56:526–528
119. McElroy SL, Hudson JI, Phillips KA, et al. Clinical and theoretical implications of a possible link between obsessive-compulsive and impulse control disorders. Depression 1993;1:121–132
120. Rasmussen SA. Commentary: obsessive compulsive spectrum disorders. J Clin Psychiatry 1994;55:89–91
121. Hollander E, Cohen LJ. Psychobiology and psychopharmacology of compulsive spectrum disorders. In: Oldham JM, Hollander E, Skodol AE, eds. Impulsivity and Compulsivity. Washington, DC: American Psychiatric Press; 1996

122. Swedo SE, Leonard HL, Rapoport JL, et al. A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). N Engl J Med 1989;321:497–501
123. Leonard HL, Lenane MC, Swedo SE, et al. A double-blind comparison of clomipramine and desipramine treatment of severe onychophagia (nail biting). Arch Gen Psychiatry 1991;48:821–827
124. Gordon CT, State RC, Nelson JE, et al. A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. Arch Gen Psychiatry 1993;50:441–447
125. Kruesi MJ, Fine S, Valladares L, et al. Paraphilias: a double-blind crossover comparison of clomipramine versus desipramine. Arch Sex Behav 1992;21(6):587–593
126. Swedo SE, Rapoport JL, Leonard HL, et al. Regional cerebral glucose metabolism of women with trichotillomania. Arch Gen Psychiatry 1991; 48:828–833
127. Phillips KA. Body dysmorphic disorders: the distress of imagined ugliness. Am J Psychiatry 1991;148:1138–1149
128. Barsky AJ. Hypochondriasis and obsessive compulsive disorder. Psychiatr Clin North Am 1992;15(4):791–801
129. Fallon BA, Klein BW, Liebowitz MR. Hypochondriasis: treatment strategies. Psychiatric Annals 1993;23(7):374–381
130. Kaye WH, Weltzin TE, Hsu LKG, et al. Patients with anorexia nervosa have elevated scores on the Yale-Brown Obsessive-Compulsive Scale. Int J Eat Disord 1992;12(1):57–62
131. Hudson JI, Carter WP, Pope HG Jr. Antidepressant treatment of binge-eating disorder: research findings and clinical guidelines. J Clin Psychiatry 1996;57(suppl 8):73–79
132. Warnock JK, Kestenbaum T. Pharmacologic treatment of severe skin-picking behaviors in Prader-Willi syndrome: two case reports. Arch Dermatol 1992;128(12):1623–1625
133. Hellings JA, Warnock JK. Self-injurious behavior and serotonin in Prader-Willi syndrome. Psychopharmacology Bull 1994;30(2):245–250
134. Christenson GA, Mackenzie TB, Mitchell JE. Characteristics of 60 adult chronic hair pullers. Am J Psychiatry 1991;148:365–370
135. Swedo SE, Leonard HI. Trichotillomania: an obsessive-compulsive spectrum disorder? Psychiatr Clin North Am 1992;15:777–790
136. DeCaria CM, Hollander E, Grossman R, et al. Diagnosis, neurobiology, and treatment of pathological gambling. J Clin Psychiatry 1996;57(suppl 8):80–84
137. McElroy SL, Keck PE Jr, Phillips KA. Kleptomania, compulsive buying, and binge-eating disorder. J Clin Psychiatry 1995;56(suppl 4):14–26
138. Black DW. Compulsive buying: a review. J Clin Psychiatry 1996;57 (suppl 8):50–55
139. Simeon D, Hollander E, Stein DJ, et al. Body dysmorphic disorder in the DSM-IV field trial for obsessive-compulsive disorder. Am J Psychiatry 1995;152:1207–1209
140. Phillips KA, McElroy SL. An open-label study of fluvoxamine in body dysmorphic disorder. Biol Psychiatry 1996;39(7):625
141. Hollander E, Cohen L, Simeon D, et al. Fluvoxamine treatment of body dysmorphic disorder. J Clin Psychopharmacol 1994;14:75–77
142. Hollander E, Cohen LJ, Simeon D. Body dysmorphic disorder. Psychiatric Annals 1993;23(7):359–364
143. Fallon BA, Liebowitz MR, Salman E, et al. Fluoxetine for hypochondriacal patients without major depression. J Clin Psychopharmacol 1993;13: 438–441
144. Thiel A, Broocks A, Ohlmeier M, et al. Obsessive-compulsive disorder among patients with anorexia nervosa and bulimia nervosa. Am J Psychiatry 1995;152:72–75
145. Pigott TA, Altemus M, Rubenstein CS, et al. Symptoms of eating disorders in patients with obsessive-compulsive disorder. Am J Psychiatry 1991;148:1552–1557
146. Kaye WH, Weltzin T, Hsu LKG. Relationship between anorexia nervosa and obsessive and compulsive behaviors. Psychiatric Annals 1993;23 (7):365–372
147. Jarry JL, Vaccarino FJ. Eating disorder and obsessive-compulsive disorder: neurochemical and phenomenological commonalities. J Psychiatry Neurosci 1996;21(1):36–48
148. Ayuso-Gutierrez JL, Palazon M, Ayuso-Mateos JL. Open trial of fluvoxamine in the treatment of bulimia nervosa. Int J Eat Disord 1994;15: 245–249
149. Spigset O, Pleym H. A case report of successful treatment of bulimia nervosa with fluvoxamine. Pharmacopsychiatry 1991;24:180
150. Gardiner HM, Freeman CPL, Jesinger DK, et al. Fluvoxamine: an open pilot study in moderately obese female patients suffering from atypical eating disorders and episodes of bingeing. International Journal of Obesity and Related Metabolic Disorder 1993;17:301–305
151. Hudson JI, McElroy SL, Raymond NC, et al. Fluvoxamine treatment of binge eating disorder: a multicenter, placebo-controlled trial. In: New Research Program and Abstracts of the 1994 American Psychiatric Association Annual Meeting; May 26, 1994; Philadelphia, Pa. Abstract NR620:218
152. Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa: a multi-center, placebo-controlled, double-blind trial. Arch Gen Psychiatry 1992;49:139–147
153. Fichter MM, Kruger R, Rief W, et al. Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. J Clin Psychopharmacology 1995;16:9–18
154. Abell CA, Farquhar DL, Galloway SM, et al. Placebo controlled double-blind trial of fluvoxamine maleate in the obese. J Psychosom Res 1986; 30:143–146
155. Flament MF, Corcos M, Igoin L, et al. Treatment of normal-weight bulimia nervosa with fluvoxamine: negative results from a double blind study with 103 outpatients. Presented at the WPA-regional symposium, "Developmental Issues in Psychiatry"; July 1994:10–14; Lisbon, Portugal
156. McDougle CJ, Kresch BA, Goodman WK, et al. A case controlled study of repetitive thoughts and behaviors in adults with autistic disorder and obsessive compulsive disorder. Am J Psychiatry 1995;152:772–777
157. McDougle CJ, Price LH, Goodman WK. Fluvoxamine treatment of coincident autistic disorder and obsessive-compulsive disorder: a case report. J Autism Dev Disord 1990;20(4):537–543
158. Harvey RJ, Cooray SE. The effective treatment of severe repetitive behaviour with fluvoxamine in a 20 year old autistic female. Int Clin Psychopharmacol 1995;10:201–203
159. Christenson GA, Crow SJ. The characterization and treatment of trichotillomania. J Clin Psychiatry 1996;57(suppl 8):42–49
160. Christenson GA, Mackenzie TB, Mitchell JE, et al. A placebo-controlled double-blind crossover study of fluoxetine in trichotillomania. Am J Psychiatry 1991;148:1566–1571
161. Streichenwein SM, Thornby JI. A long-term, placebo-controlled crossover trial of the efficacy of fluoxetine for trichotillomania. Am J Psychiatry 1995;152:1192–1196
162. Hollander E, Frenkel M, DeCaria C, et al. Treatment of pathological gambling with clomipramine [letter]. Am J Psychiatry 1992;149:710–711
163. Wong CM, Hollander E. New dimensions in the OCD spectrum: autism, pathologic gambling, and compulsive buying. Primary Psychiatry 1996: 20–26, 29–34
164. McElroy SL, Keck PE Jr, Pope HG Jr, et al. Compulsive buying: a report of 20 cases. J Clin Psychiatry 1994;55:242–248
165. Black DW. The case of the women who couldn't stop shopping. Menninger Letter 1995;3:3
166. Travin S. Compulsive sexual behaviors. Psychiatr Clin North Am 1995; 18(1):155–169
167. Stein DL, Hollander E, Anthony DT, et al. Serotonergic medications for sexual obsessions, sexual addictions, and paraphilias. J Clin Psychiatry 1992;53:267–271
168. Zohar J, Kaplan Z, Benjamin J. Compulsive exhibitionism successfully treated with fluvoxamine: a controlled case study. J Clin Psychiatry 1994;55:86–88
169. Dominguez RA, Goodnick PJ. Adverse events after the abrupt discontinuation of paroxetine. Pharmacotherapy 1995;15(6):778–780
170. Frost L. Shock-like sensations after discontinuation of selective serotonin reuptake inhibitors [letter]. Am J Psychiatry 1995;152:810
171. Barr LC, Price LH, Goodman WK. Physical symptoms associated with paroxetine discontinuation [letter]. Am J Psychiatry 1994;151:289
172. DeBattista C, Shatzbert AF. Physical symptoms associated with paroxetine withdrawal. Am J Psychiatry 1995;152:1235–1236
173. Bloch M, Stager SV, Braun AR, et al. Severe psychiatric symptoms associated with paroxetine withdrawal [letter]. Lancet 1995;346:57
174. Phillips SD. A possible paroxetine withdrawal syndrome [letter]. Am J Psychiatry 1995;152:645–646
175. Pyke RE. Paroxetine withdrawal syndrome [letter]. Am J Psychiatry 1995;152:149–150
176. Keuthen NJ, Cyr P, Ricciardi JA, et al. Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine. J Clin Psychopharmacol 1994;14:206–207
177. Mallya G, White K, Gunderson C. Is there a serotonergic withdrawal syn-

drome [letter]? Biol Psychiatry 1993;33:851–852
178. Black DW, Wesner R, Gabel J. The abrupt discontinuation of fluvoxamine in patients with panic disorder. J Clin Psychiatry 1993;54:146–149
179. Szabadi E. Fluvoxamine withdrawal syndrome. Br J Psychiatry 1992; 160:283–284
180. Louie AK, Lannon RA, Luriko JA. Withdrawal reaction after sertraline discontinuation. Am J Psychiatry 1994;151:450–451
181. Leiter FL, Nierenberg AA, Sanders KM, et al. Discontinuation reactions following sertraline. Biol Psychiatry 1995;38:694–695
182. Lauterbach EC. Fluoxetine withdrawal and thalamic pain. Neurology 1994;44:983–984
183. Stoukides JA, Stoukides CA. Extrapyramidal symptoms upon discontinuation of fluoxatine [letter]. Am J Psychiatry 1991;148:1263
184. Einbinder E. Fluoxetine withdrawal? [letter] Am J Psychiatry 1995;152: 1235
185. Bergeron R, Blier P. Cisapride for the treatment of nausea produced by selective serotonin reuptake inhibitors. Am J Psychiatry 1994;151:1084–1086
186. Wiseman LR, Faulds D. Cisapride: an updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. Drugs 1994;47:116–152
187. Aapro MS. 5-HT3 receptor antagonists: an overview of their present status and future potential in cancer therapy-induced emesis. Drugs 1991; 42:551–568
188. Propulsid (cisapride). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1997:1300–1301
189. Nierenberg AA, Adler LA, Peselow E, et al. Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994;151:1069–1072
190. Pigott TA, L'Heureux F, Rubenstein CS, et al. A double-blind, placebo controlled study of trazodone in patients with obsessive-compulsive disorder. J Clin Psychopharmacol 1992;12:156–162
191. Gitlin MJ. Psychotropic medications and their effects on sexual function: diagnosis, biology, and treatment approaches. J Clin Psychiatry 1994;55: 406–413
192. McCormick S, Olin J, Brotman AW. Reversal of fluoxetine-induced anorgasmia by cyproheptadine in two patients. J Clin Psychiatry 1990;51: 383–384
193. Zajecka J, Fawcett J, Schaff M, et al. The role of serotonin in sexual dysfunction: fluoxetine-associated orgasm dysfunction. J Clin Psychiatry 1991;52:66–68
194. Arnott S, Nutt D. Successful treatment of fluvoxamine-induced anorgasmia by cyproheptadine. Br J Psychiatry 1994;164:838–839
195. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. J Clin Psychiatry 1991;52:163–164
196. Hollander E, McCarley A. Yohimbine treatment of sexual side effects induced by serotonin reuptake blockers. J Clin Psychiatry 1992;53:207–209
197. Jacobson FM. Fluoxetine-induced sexual dysfunction and an open trial of yohimbine. J Clin Psychiatry 1992;53:119–122
198. Balogh S, Hendricks SE, Kang J. Treatment of fluoxetine-induced anorgasmia with amantadine [letter]. J Clin Psychiatry 1992;53:212–213
199. Labbate LA, Pollack MH. Treatment of fluoxetine-induced sexual dysfunction with bupropion: a case report. Ann Clin Psychiatry 1994;6(1):13–15
200. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holiday. Am J Psychiatry 1995;152: 1514–1516