New Developments in the Treatment of Obsessive-Compulsive Disorder

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The treatment of obsessive-compulsive disorder (OCD) has changed dramatically in the last 10 years. Currently, the serotonin reuptake inhibitors (SRIs) and the serotonin selective reuptake inhibitors (SSRIs) are considered the "first choice" agents for pharmacologic treatment of OCD, although few head-to-head comparisons exist between any two specific agents. Strategies for nonresponders and partial responders to the SRI/SSRIs are reviewed. The only agents that have shown significant improvement as augmenting agents to an SRI/SSRI in systematic trials have been clonazepam and haloperidol. Predictors of response to pharmacotherapy have been limited, but several reports have found that an early age at onset of OCD has been associated with a poorer response to medications. Long-term maintenance medication may be necessary for some, although behavioral therapy may improve the need for extended pharmacotherapy. Cognitive behavioral therapy, specifically exposure with response prevention, still remains an effective and important component of treatment for many. One of the newest developments is the identification of a pediatric subtype of OCD characterized by prepubertal acute onset after group A beta-hemolytic streptococcal pharyngitis. Investigation trials with these children include immunomodulatory therapies and penicillin treatment and prophylaxis. If a unique subgroup of children with OCD can be identified, then novel treatments may prove effective and have a role in long-term prophylaxis. *(J Clin Psychiatry 1997;58[suppl 14]:39–45)*

The treatment of obsessive-compulsive disorder (OCD), perhaps more than for any other disorder, has changed dramatically in the last 10 years. The development of the serotonin reuptake inhibitor (SRI) class of medications and of the specialized cognitive-behavioral therapies, coupled with an increasing neurobiological line of study into underlying mechanisms, has revolutionized our understanding about the causes and the treatment of OCD. Although OCD symptoms have been described for centuries, effective treatments have generally not been available, and the long-term outcome of patients has been generally chronic. With the development of new pharmacotherapeutic agents, attention has now focused on the need for long-term maintenance, on their safety and efficacy in the pediatric ages, and their applicability in other compulsive-like (spectrum) disorders. Investigations into etiology and possible subtypes of OCD have suggested that potential subtypes merit study.

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The introduction of the SRIs and the serotonin selective reuptake inhibitors (SSRIs) has had a major impact on the pharmacologic treatment of OCD. Although reports of clomipramine's efficacy for OCD were published 20 years ago,[1] it was not until the late 1980s that any SRIs or SSRIs were available in the United States. The mid-1980s saw investigational trials of clomipramine for adults and for adolescents with OCD, and during that time many patients sought participation in research trials for treatment. Clomipramine was approved by the Food and Drug Administration (FDA) in 1989 for the treatment of OCD in patients aged 12 years or over. The large multicenter trial (21 sites) of clomipramine versus placebo (parallel design) reported the superiority of clomipramine, and interestingly, there was little placebo response, unlike that which had been typically reported in investigational antidepressant trials for depression.[2] Similar efficacy was reported in 23 adolescents in a double-blind, placebo-controlled crossover study,[3] along with a side effect profile similar to that seen in adults.

Studies of the specific efficacy of clomipramine, a potent SRI, in addition to challenge studies (using a serotonergic agonist), led to the "serotonin hypothesis" of OCD.[4] Although OCD is hypothesized to be a manifestation of a primary serotonin dysregulation, multiple neurotransmitters (particularly those associated with serotonergic and dopaminergic activity) are most likely involved in the cause of OCD.[5,6]

The specific efficacy of clomipramine for OCD, which had not been demonstrated previously over that with other tricyclics, was attributed to its potent serotonergic properties. To study the specificity of clomipramine, a 10-week double-blind crossover comparison of clomipramine and desipramine (a selective noradrenergic reuptake inhibitor) was completed in 48 children and adolescents with OCD.[7] Desipramine was chosen as the comparison drug because it is primarily noradrenergic in action but has similar antidepressant and anxiolytic effects. Clomipramine was significantly better than desipramine in ameliorating the OCD symptoms at Week 5, and desipramine was no more effective in improving OCD symptoms than placebo had been in the earlier study.[3] In fact, when desipramine was given as the second active medication, many of the patients relapsed. The superiority of clomipramine over other tricyclics to treat OCD appeared clear. Interestingly, clomipramine's first metabolite, desmethylclomipramine, is a potent noradrenergic reuptake inhibitor. This led to speculation as to whether some balance or combination of neurotransmitters might be involved.

The availability of clomipramine for investigational study for OCD and its efficacy spurred development of SSRIs. To date, large systematic trials of SSRIs in patients with OCD have been reported for fluoxetine, fluvoxamine, sertraline, and paroxetine.[8–11] To date, clomipramine, fluoxetine, paroxetine, sertraline, and fluvoxamine have an FDA indication for the treatment of OCD. Sertraline has depression as an FDA-approved indication and is under study for OCD. Clomipramine is approved for individuals 12 years and older, and the others are under study in the adolescent age group. Initial reports suggest that the SSRIs have an efficacy and side effect profile in children and adolescents generally similar to that seen in adults.

COMPARISONS WITHIN THE SRIs/SSRIs

The SSRIs are a new class of antidepressants with distinct advantages in their side effect profile and their broad therapeutic index over that seen with the tricyclic antidepressants. The SSRIs differ among themselves, just as they do when compared with clomipramine, on specific pharmacokinetic properties, which impact practically on issues of dosage, therapeutic monitoring, side effect profile, and drug-drug interaction. For this discussion of the treatment of OCD, the differences between the specific agents, in terms of their efficacy, pharmacokinetic properties, and safety, are emphasized.

The serotonergic agents differ in potency and selectivity. The agents with the most potent serotonergic reuptake inhibition (in order of decreasing potency) are paroxetine, fluvoxamine, sertraline, clomipramine, and fluoxetine.[12] Paroxetine is the most selective (norepinephrine to serotonin reuptake inhibition ratio) of the SRIs/SSRIs, followed by sertraline, fluvoxamine, fluoxetine, and clomipramine.[12] Despite these comparisons, between these agents, neither the potency nor selectivity profile appears to be correlated with clinical antiobsessional efficacy. These become important issues for considering dosages, side effects, and drug interactions.

Which SRI is the most effective for treating OCD? Unfortunately, this has not been clearly answered. There are only a few direct ("head-to-head") comparisons of two agents, and these are typically limited by methodological issues (e.g., small sample size, crossover design and carryover effect, inclusion of previous nonresponders, specific dosages, and side effects). Pigott and colleagues[13] reported that 11 subjects did not have significantly different clinical responses when on 10 weeks of clomipramine therapy versus 10 weeks of fluoxetine (4-week washout between medications). Similarly, Freeman and colleagues[14] did not report a difference in efficacy in the double-blind comparison of clomipramine and fluvoxamine in a 10-week parallel-design (N = 34 fluvoxamine, N = 30 clomipramine) study.

With limited direct comparison, meta-analyses across studies have been attempted. One must remember that intent-to-treat comparisons (of all subjects enrolled, as opposed to just those completing a trial) are most accurate. Thus, dropouts cannot be omitted from analyses, and dropouts need to be examined in terms of whether there are more dropouts on one medication (e.g., due to side effects), which would affect the conclusions about those who completed a trial. The largest and most systematic comparison consisted of the data from the multicenter placebo-controlled trials of clomipramine, fluvoxamine, fluoxetine, and sertraline submitted to the FDA. Greist and colleagues[15] reported that clomipramine was more effective than the SSRIs when compared by intent-to-treat analyses. The three SSRIs appeared comparable among themselves in terms of efficacy. Interestingly, although clomipramine was the most anticholinergic of all the agents, there were no more dropouts from the clomipramine group than from the others. Reports of other meta-analyses, when assessed using intent-to-treat analyses, found that clomipramine was more effective than the comparison SSRI.[16–18] These studies would suggest that clomipramine may be more effective, although direct comparisons are necessary before this can be concluded. Currently, the SRI clomipramine and the SSRIs are considered the "first choice" for pharmacologic treatment of OCD. Some of the newer agents, venlafaxine, which has both SRI and noradrenergic reuptake inhibition properties, and nefazodone, a serotonergic agonist, have been insufficiently studied to determine their role in the treatment of OCD.

WHICH TO CHOOSE?

Even after weighing FDA indications and the published controlled literature, the prescribing physician is left with

choosing from the SRI/SSRI family, which includes clomipramine, fluoxetine, sertraline, paroxetine, and fluvoxamine. Often, the side effect profile becomes the primary consideration for the first trial. Although clomipramine has been the most extensively studied, and some evidence previously discussed suggests that it may be more effective, it has the most anticholinergic side effect profile of the agents. This may be desirable for individuals who require a more sedating medication at bedtime or during the day. However, in an individual with any medical concern for whom anticholinergic side effects are not desirable, an SSRI would be chosen instead. In patients with a high risk of suicide, clomipramine would not be the first choice of agents, since, as a tricyclic, it can potentially be very toxic in overdoses. In contrast, the SSRIs offer a less anticholinergic side effect profile, but may be associated with more complaints of headaches, nausea, insomnia, and agitation. As previously discussed, the studies report a similar dropout rate, whether the subjects were taking clomipramine or an SSRI.[15] In one of the few direct comparisons of clomipramine and fluvoxamine, both agents were well tolerated; subjects taking fluvoxamine reported fewer anticholinergic side effects and less sexual dysfunction but more headache and insomnia than those taking clomipramine.[14]

Other considerations might include comorbidity. Comorbid diagnoses may suggest either for or against the choice of a tricyclic, but this is not typically a major consideration. With the increasing use of concomitant medications and the recent attention to hepatic metabolism, the competitive inhibition profile of the specific P450 enzyme system by each of the medications has been under study. Thus, the potential interaction of any two medications, based on the enzyme system typically involved in the metabolism of each of the agents, should be weighed in the choice of a medication. In conclusion, the large controlled trials do not lead to immediate recommendations as to which specific SRI/SSRI should be chosen for any one individual. Consideration of comorbid psychiatric disorders, medical issues, side effects, concomitant medications, and previous trials lead to an individual decision for each patient.

DOSE AND DURATION OF PHARMACOTHERAPY

Adequate dose and duration of a serotonergic medication are required to determine whether an individual is a responder or nonresponder to a specific agent. Although this guideline is still thought to be important, thinking has changed somewhat on the rate of increasing the dosage and on the dosage of the SRI/SSRIs used. Traditionally, the literature has emphasized the necessity of a higher dosage to achieve a response. The multicenter trials of the SRI/SSRIs used dosages that are now considered to be on the "high end." For example, the mean dosages in the large trials were 225 mg/day for clomipramine[2] and 283 mg/day for fluvoxamine[9]; however, the study design did not allow for any conclusions about the efficacy of lower dosages. The studies of fluoxetine and sertraline included a fixed-dose design of different dosages. Interestingly, fluoxetine at 20, 40, and 60 mg/day was effective; however, there were many more dropouts at the higher dosages.[8] Similarly, sertraline was effective at 50, 100, and 200 mg/day, but dropouts were greater at the higher dosages.[11] This may explain the anecdotal clinical observation that lower dosages are needed in the long run for maintenance.

Given these studies with a flat dose-response curve, coupled with the increased rate of side effects with increased dosage, a slower escalation using a lower minimal dosage has achieved some favor. Dosages (per day) targeted in the multicenter trials included clomipramine 250 mg, fluoxetine 60 mg, sertraline 200 mg, fluvoxamine 300 mg, and paroxetine 60 mg. Although the old adage "adequate dosage for a long enough trial" still holds, a more minimal initial dose is often attempted for the desired optimal therapeutic effect. With a lower initial dosage, the patient can tolerate the side effects and increases can be done slowly and steadily. Most importantly, a sufficient duration of treatment is required to determine whether a patient will be able to respond or not. Generally, at least a 10-week trial of an SRI/SSRI is required before one can conclude that the patient has not responded. Not uncommonly, patients who have an initial response may continue to experience improvement for several months.[15]

RESPONDERS AND NONRESPONDERS

In practice, the clinician may often have to decide the next step when a patient has had either no response or a partial response to an SRI/SSRI at 10 to 12 weeks. The clinician has to decide whether to recommend switching to another SSRI or utilizing the addition of an augmenting agent. There are no systematic studies that have compared these two options.

Generally, if an individual has had no response to the SSRI at 10 to 12 weeks, then another SSRI may be attempted. Failure to respond to one SSRI does not necessarily predict failure to respond to another SSRI. In the multicenter fluvoxamine trial, 19% of the patients who had failed a previous trial (specifically, clomipramine or fluoxetine) did respond to fluvoxamine.[9] The interpretation of these data is complicated by the issue that the more recent SSRI multicenter trials contained more treatment nonresponders than earlier studies. (The initial investigational trials of clomipramine in the 1980s had not enrolled individuals who had failed to respond to SRI/SSRIs, since other agents were unavailable.) Although no systematic trials have been conducted to compare switch versus augmentation strategies, general clinical experience would support a change of medications for the nonresponder.

In contrast, patients who have experienced a partial clinical response in the initial 10 to 12 weeks are often considered for augmentation strategies and a longer trial of the specific SSRI. Unfortunately, augmentation strategies have been somewhat disappointing. Nearly every class of psychotropic medications has been tried in an open fashion, but only four augmenting agents have had controlled trials. Clonazepam, haloperidol, lithium, and buspirone have been studied systematically, and only clonazepam and haloperidol have proved to be superior to placebo in these controlled augmentation trials. Pigott and colleagues[19] reported that in a double-blind, placebo-controlled crossover augmentation study of 18 patients who were taking either clomipramine or fluoxetine, clonazepam augmentation produced some significant improvement. McDougle and colleagues[20] reported that of the 34 OCD patients taking fluvoxamine who participated in a 4-week double-blind haloperidol (6 mg/day) augmentation trial, 11 of the 17 in the haloperidol group responded and none of the 17 in the placebo group did. Of note, a comorbid tic disorder was associated with the positive augmentation response. Two controlled trials of lithium augmentation[21,22] and three controlled trials of buspirone augmentation[23–25] did not find the augmentation strategies superior to placebo.

In conclusion, the systematic trials support the use of clonazepam or haloperidol as considerations in augmentation strategies. Obviously, issues of side effects and drug interactions must be weighed. The concerns about the use of benzodiazepines include the need to avoid abrupt discontinuation, as well as observation for symptoms of depression, irritability, and disinhibition, albeit rare.[26] Augmentation with neuroleptics may be considered in patients with a comorbid tic disorder or with a schizotypal personality disorder.[27] Concerns about the use of neuroleptics include cognitive impairment, extrapyramidal symptoms, including tardive dyskinesias, as well as their increased incidence of side effects with concomitant pharmacotherapeutic agents. There may be individuals who experience an improvement on other specific augmentation agents; however, only controlled trials are presented here.

PREDICTORS OF RESPONSE

Attempts to identify predictors of treatment response have been generally limited and inconsistent. Methodological issues that complicate the identification of specific factors may include small sample size, homogeneous groups, and statistical limitations.[28] In the controlled clomipramine pediatric trial, neither age, sex, severity and duration of symptoms, concomitant depressive symptoms, nor symptom pattern predicted medication response.[7] The long-term follow-up of the same children and adolescents (at 2 to 7 years) reported that a poorer long-term outcome was related to a higher OCD symptomatology score after 5 weeks of treatment (but not at baseline) and presence of a lifetime history of a tic disorder and of parental Axis I psychiatric diagnosis.[29] Others have also reported that patients with a comorbid tic disorder may not respond as well to the SSRIs.[20]

In an analysis of 520 adults who had participated in the clomipramine treatment trials, age at onset was a strong predictor of response to clomipramine. Individuals who developed OCD later in life had a better chance of responding to medication than those who became ill earlier, and this was independent of duration of illness.[28] Although the pediatric studies did not find that age at onset predicted response,[3,7] this might be explained by the fact that all had pediatric onset of symptoms. In the adult report, the age at onset of OCD symptoms ranged from 3 to 62 years, and in that heterogeneous group the association was found. In a report of 53 adults with OCD, a lower age at onset and longer duration of disorder were both associated with poorer response to treatment.[29] Additionally, the presence of concomitant schizotypal personality disorder predicted poor drug response in a stepwise multiple regression.[29] These reports are consistent with Swedo and colleagues' reports[30–32] that early-onset pediatric OCD may represent a distinct subgroup of OCD that may be distinct and may require unique treatments.

LONG-TERM MAINTENANCE

The issue of how long to continue an individual, who has responded to an SRI/SSRI, on medication maintenance is debated. Although periodic discontinuation trials are advisable, many responders require ongoing maintenance pharmacotherapy. In the only double-blind discontinuation study, Leonard and colleagues[33] designed a 2-month desipramine substitution phase in an 8-month study of children and adolescents on long-term clomipramine maintenance. Desipramine was chosen to avoid any tricyclic withdrawal syndrome and to truly blind the subjects and raters as to whether a medication was prescribed (e.g., placebo would be more likely to be identified as such). Eight of 9 patients who were switched to desipramine relapsed within the 2 months of substitution, as compared to only 2 of 11 who continued to take clomipramine.[33] Of note, even patients on continued clomipramine maintenance continued to exhibit some obsessive-compulsive symptoms, which varied in severity over time. It is not known how this is comparable to adults on long-term maintenance. Pato and colleagues[34] reported that 89% of subjects who had placebo substituted for clomipramine during maintenance relapsed within 7 weeks. Similarly, the majority of patients on fluoxetine maintenance relapsed within 12 weeks of discontinuing medication.[35] These studies would suggest that long-term maintenance is required for many, although many are optimistic that cognitive-behavioral therapy may decrease the need for long-term pharmacotherapy.

OTHER TREATMENTS

Several authors have reported the efficacy of intravenous clomipramine in small open trials.[36–38] Typically, intravenous clomipramine was given daily for 2 to 6 weeks to patients who did not respond or could not tolerate oral clomipramine. Fallon and colleagues[37] reported a 39% decrease of OCD symptoms in 3 of 5 patients after 14 weekdays of intravenous clomipramine; Warneke[36] reported a similar response. Recently, Koran and colleagues[38] administered intravenous clomipramine in five adults for 6 to 7 weeks, and found generally positive results by 3 to 4 weeks, and all subjects were on maintenance oral clomipramine at 6- to 12-month follow-up. Speculation about how this treatment might work includes rapid down-regulation of serotonergic receptors and/or decreasing first-pass hepatic metabolism and thereby increasing the clomipramine:metabolite ratio (increasing relative potency of serotonin reuptake inhibition). This route would still be considered investigational and might be considered for nonresponders or for those who could not tolerate the side effects of oral medication.

Historically, treatment interventions for severe OCD included psychoanalysis and psychosurgery. More recently with improved techniques and clearer knowledge about anatomical location, the psychosurgery or neurosurgery techniques, which have included anterior capsulotomy, anterior cingulotomy, and subcaudate tractotomy, have proved effective for some with severe and intractable OCD.[39] The development of the gamma knife, which does not require any kind of surgical opening of the skull, has been studied in patients who have failed aggressive pharmacotherapy and behavioral therapy. A placebo-controlled investigation is ongoing for this specific, and select, group of patients.

Cognitive-behavioral therapy, specifically the "exposure with response prevention" model, has been proved to be an effective treatment in individuals with OCD. This specific technique for the OCD patient was developed in England by Isaac Marks[40] and has been modified over the last 10 years. The exposure component is based on the fact that anxiety usually attenuates after sufficient duration of contact with the feared object. Response prevention blocks the rituals or avoidance behavior, and it typically is an extinction procedure.

Although both pharmacotherapy and behavior therapy have each been shown to be effective treatments of OCD, direct comparisons of the two approaches are few and often limited by methodological issues. Cox and others[41] reported a meta-analysis of 25 treatment studies that had used either clomipramine, fluoxetine, or exposure-based behavior therapy and concluded that all three treatments were effective. Others have reported similar findings from a meta-analysis.[16] One advantage that may be offered by behavior therapy is that relapse is less frequent and may not occur as soon as therapy is stopped.[42] The relative merits of pharmacotherapy versus behavior therapy are debated, yet both offer effective treatment and are often utilized together. One of the most exciting reports was that of Baxter and colleagues[43] who found that both medication and behavior therapy produced similar changes in brain metabolism in patients with OCD who were given one of the treatments. This would suggest that effective treatments are powerful interventions, the effects of which can be measured on dynamic brain metabolism scans, regardless of which treatment was chosen. Certainly, this merits more study. With the development of systematic manuals that can be used at many sites,[44] some of the methodological issues of studying different techniques at different sites can be decreased.

Investigations continue to identify safe and effective treatments for OCD. Currently, the combination of an SRI/SSRI and behavior modification is often used. Although this is effective for most, there are still individuals who do not respond. Alternative treatments are receiving attention.

NEW DEVELOPMENTS

One of the most exciting new lines of treatment is based on the identification of a pediatric subtype of OCD. Parallel lines of research on Sydenham's chorea (the neurologic variant of rheumatic fever) and on pediatric OCD and Tourette's syndrome led to the development of a subgroup of children who developed their OCD and/or tic disorder after group A beta-hemolytic streptococcal (GABHS) pharyngitis.[30–32,45,46] Swedo and colleagues[30–32] at the National Institute of Mental Health had described that children with Sydenham's chorea developed OCD acutely with the illness and that the OCD remitted after the chorea resolved. This led to the conceptualization of Sydenham's chorea as a medical model of OCD, and it was consistent with ongoing work on the basal ganglia dysfunction hypothesized to be etiologic in OCD. Successful immunomodulatory treatment of Sydenham's chorea led to the development of similar treatment protocols for children with GABHS-related OCD and tic disorders, which were felt to be a manifestation of autoimmune neuropsychiatric disorders.

Preliminary results of immunomodulatory therapies, including plasmapheresis and intravenous immunoglobulin, described significant improvement in children who had an underlying autoimmune basis to the triggering of their illness.[32] The treatment trial is ongoing and enrolls prepubertal children who have had an abrupt onset or exacerbation of OCD and/or tic disorder after infections. (Lorraine Lougee, L.C.S.W.-C., or Marjorie Garvey, M.D., at NIMH can be contacted at 301-496-5323 for information.) Additionally, a double-blind crossover trial of penicillin prophylaxis (4 months of placebo and 4 months of penicillin) for children in whom OCD or tic disorder

symptoms are precipitated or exacerbated by GABHS is ongoing. If a unique subgroup of children with OCD and/or tic disorders can be identified, novel treatments (immunomodulatory and antibiotic) may be effective and may ultimately prove to have a role in long-term maintenance and prophylaxis.

Drug names: buspirone (BuSpar), clomipramine (Anafranil), clonazepam (Klonopin), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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Disclosure of Off-Label Usage

The following agents mentioned in this article are *not* indicated for obsessive-compulsive disorder: buspirone, clonazepam, haloperidol, intravenous immunoglobulins, lithium, nefazodone, penicillin, plasma pheresis, venlafaxine, and intravenous administration of clomipramine.

Discussion

Dr. Keller: Given what appears to be the comparatively refractory, chronic nature of obsessive-compulsive disorder (OCD), your review should stimulate discussion.

Dr. Gorman: All of us are skeptical of hypotheses about disorders that involve a single neurotransmitter, but I am convinced about the serotonergic hypothesis of OCD because a number of patients with schizophrenia who are treated with clozapine or risperidone (both powerful 5-HT_2 receptor blockers) develop OCD for the first time, and then respond when they begin taking sertraline.

Clomipramine may be more effective than SSRIs for OCD, and the primary metabolite of clomipramine is norclomipramine, which is a potent noradrenergic reuptake blocker. There's some evidence in the biological psychiatry literature about a noradrenergic defect or abnormality in OCD patients. There may be added benefit in targeting both neurotransmitters.

I don't know if everybody here is convinced that trichotillomania responds well to SSRIs. A controlled trial in *The American Journal of Psychiatry* recently reported a completely negative finding [Streichenwein SM, Thornby JI. Am J Psychiatry 1995;152:1192–1196].

Dr. Leonard: You're absolutely right. When somebody comes into your office with OCD, you feel like you have a chance, but when somebody comes in with trichotillomania, you steel yourself because you know it will be challenging to treat.

We have a body of evidence suggesting that there may be a relationship between trichotillomania and OCD. The first-degree relatives of probands with trichotillomania have an increased rate of OCD, and certainly we often see patients who have symptoms of both. But trichotillomania feels like a different disorder, partly because it's not as egodystonic as OCD. OCD patients say, "I'm really distressed by my thoughts. I'll do anything to get rid of them." There is a self-soothing, more ego-syntonic feeling that patients with trichotillomania describe. I use an SRI and behavior modification. There is no doubt in my mind that patients with trichotillomania are much more difficult to treat, but I'm not sure why they're much more difficult to treat.

Dr. Hirschfeld: Do you not feel the same way about OCD patients?

Dr. Leonard: Clinicians have more leeway with OCD. I usually tell clinicians to expect the best results with a combined approach: a serotonin reuptake inhibitor (SRI) and cognitive-behavioral therapy (exposure with response prevention). In reality, patients usually either do or do not want to try an SRI; those who refuse an SRI often agree to cognitive-behavioral therapy. Most patients will be offered one or the other, but they should have both.

Dr. Gorman: Trichotillomania patients have few obsessions compared with the average OCD patient. Some old literature reports that clomipramine is more useful for obsessions than compulsions. I have always wondered if the lack of obsessions in trichotillomania was one reason why it seemed to be less clearly drug responsive.

Dr. Leonard: My colleagues and I reported the first systematic trial of clomipramine for trichotillomania [Swedo SE, Leonard HL, Rapoport JL, et al. N Engl J Med 1989;321:497–501], and found that clomipramine was superior to placebo. Then Michael Jenike, M.D., wrote the editorial about the obsessive-compulsive-spectrum disorders, which opened up the area. Just recently, we published a letter to the editor in the *New England Journal of Medicine* following up on what happened to the patients from that first study [Swedo SE, Lenane MC, Leonard HL. N Engl J Med 1993;329:141–142]. They had a fairly poor outcome. In some ways, even though you can show in a systematic trial that an SRI works, the adult women with trichotillomania in our study were more treatment-refractory, more disabled, and ill for a longer time than most trichotillomania patients.

Dr. Yonkers: Some of the European work on intravenous clomipramine and A. J. Allan's studies also suggest that the ratio of clomipramine to its metabolites may be important. On occasion, I've found that mixing clomipramine with one of the SRIs, particularly fluoxetine or sertraline, turns a nonresponder to a responder. I wonder whether that may be an effect of the cytochrome P4503A3 or 3A4 inhibition. The effects would be similar to those with intravenous clomipramine administration.

Dr. Leonard: That's an interesting question, because some clinicians report anecdotally that some patients respond better to a combination of two SRIs. Because I often work with children, I tend to be a extremely cautious about using combined treatment because of the possibility of competitive inhibition. Obviously, when clomipramine and fluoxetine are combined, the result is a much higher serum level of fluoxetine. Mechanistically, using combination therapy raises an interesting question: are you increasing serotonergic or noradrenergic effects?

Dr. Weinreb: I occasionally see obsessive-compulsive symptoms in the context of organic dementia, such as Alzheimer's disease. Is there evidence that clomipramine would be more useful? Clomipramine, it would seem to me, would worsen Alzheimer's dementia.

Dr. Leonard: There's no real evidence to suggest that clomipramine or an SRI would be more effective. Some work suggests that the obsessions that sometimes develop in the early stages of Huntington's disease respond to SRI

treatment. However, I'm not convinced in my own clinical practice that one treatment is better than the other.The data are not available. Acral lick is a condition in which dogs lick their paws raw and lick off all their hair. Judith Rapoport, M.D., has found in controlled trials that both clomipramine and fluoxetine are effective in dogs with acral lick, which is the animal model for OCD. Those observations are interesting in understanding the causes of OCD.

Dr. Popper: Acral lick is a specific uncommon syndrome in dogs. The more common problem is "hot spots," where a dog worsens a sore area by continuing to lick it. This does not respond to antiobsessional drugs.

Dr. Leonard: We didn't get a chance to delve much into the associated disorders, but a compelling body of literature suggests that SRIs have a role in autism and pervasive developmental disorder because repetitive behaviors such as head banging are a major problem.

While there is a group of case reports about patients who became aggressive or developed self-injurious behavior while taking an SRI, far more literature supports using an SRI to treat aggression and self-injurious behavior.

Dr. Keller: Are there data available on gamma knife surgery?

Dr. Leonard: In a study at Rhode Island Hospital at Brown University, Steven A. Rasmussen, M.D., is conducting a large ongoing trial of psychosurgery treatment of OCD, using the gamma knife. Historically, the only available treatment of OCD was psychosurgery, and a large body of literature exists on the efficacy of psychosurgery. Capsulotomy, or cingulectomy, is socially much more tolerated in Europe and Sweden than in the United States and the study sample is large.

Now a protocol to use the gamma knife for psychosurgery for OCD has been approved for Brown. Inclusion criteria require that the patient has failed every standard treatment including SRIs and behavior modification and that the condition is severe enough to merit that kind of intervention. Because the gamma knife does not require opening the skull, it is possible to do sham placebo-controlled interventions, which are under way. I understand that the investigators have selected a conservative procedure and that, as a result, some patients have required two treatments. However, many of these patients have shown substantial improvement.

Dr. Keck: What's the target?

Dr. Keller: They're going after the anterior limb of the interior capsule. The earliest data were reviewed favorably after a National Institutes of Health (NIH) special site visit. The neurosurgeon doing the surgery is from the Karolinska Institute where the procedure was developed. Even though the research received a fundable priority score, the NIH reviewers denied funding on the grounds that the observation period to acquire safety data and outcome for those in the pilot study was inadequate. The safety data from Sweden were not acceptable to the reviewers. The initial cohort of about 15 patients has now been followed for almost 2 years. There have been no adverse effects on personality or neuropsychologic function. We're optimistic about securing funding for a trial with a sufficient number of subjects to obtain statistically significant results.

Interestingly, when the presentations were made, we invited the boards of trustees of two hospitals, who represent a cross-section of the lay population, because we wanted them to have an opportunity to voice concerns if they had any. They were quite excited, and none reacted in horror.

Dr. Hirschfeld: Have the OCD symptoms improved in these patients?

Dr. Keller: The researchers began with one third of the dose normally used in Sweden. Less than 10% improved with this initial dose. However, after a second dose had been administered 40% experienced significant improvement in symptoms and quality of life ratings.

Dr. Hirschfeld: Of those who do respond, does the response persist?

Dr. Leonard: Yes.