INTRODUCTION

Obsessive-compulsive disorder (OCD) is classified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as an anxiety disorder, although phenomenological and neurobiological characteristics differentiate it from other anxiety disorders. Anxiety is arguably not central to OCD, rather, is more its byproduct. The DSM-IV attempted to functionally connect obsessions and compulsions with anxiety by suggesting that obsessions induce anxiety and compulsions reduce anxiety. The core symptoms of OCD are ideas, images, or urges that are labeled as obsessions, and compulsions, which are behavioral or cognitive rituals. The boundaries of obsessions and compulsions are amorphous and nuanced, leading to considerable challenges in their clinical delineation. Thus, obsessions are inappropriate cognitions that repetitively intrude the mind, and are usually recognized by the patient as excessive and unreasonable. Obsessions as images are less common and can be confused with hallucinations. Obsessions as urges overlap with premonitory sensations in Tourette’s disorder and with impulses in impulse-control disorders. The structural characteristics of obsessions beyond their “senseless” nature are also seen in the worry experienced by

ABStract - Obsessive-compulsive disorder (OCD) is an anxiety disorder that commonly presents comorbidly with other psychiatric disorders. The underlying neurobiology of OCD is associated with circuits involving the basal ganglia, thalamus, and the frontal cortex. Randomized, placebo-controlled trials indicate acute and long-term efficacy of potent selective serotonin reuptake inhibitors (SSRIs), such as paroxetine. There is suggestive evidence that higher doses of paroxetine than those used in major depression are needed for benefit in OCD. Because of their safety and beneficial adverse-event profile, the SSRIs have become the leading choice in the pharmacological management of OCD. Psychopharmacology Bulletin. 2003;37(Suppl1):89-96.

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patients with generalized anxiety disorder (GAD) and in the ruminations of patients with major depression. In worry, the cognitions are sensible but exaggerated, while the content of ruminations is negative in relationship to the self, the past, and the future.

Compulsions are by definition driven and repetitive, but not all such behaviors are compulsive. Thus, impulses in impulse-control disorders have similar properties. Substance use disorders, paraphilias, and certain eating disorders are examples of impulse-control disorders, as are kleptomania and trichotillomania. The essential characteristic of compulsions that differentiates them from impulsive behaviors is not their obligatory nature, but the motivational drive behind them. Compulsions aim to counter obsessions, whereas impulsive behaviors relieve tension and are often gratifying, if not pleasurable. The individual resists the impulses more because of negative social consequences. Repetitive behaviors also are evident in habits, such as nail biting. Habits are infrequently driven and are often performed without conscious focus, such as while otherwise mentally preoccupied. Habit behaviors are soothing, but not pleasurable, and may be increased with anxiety.

Why is there overlap among these phenomena and consequent confusion in our nomenclature? What does our increasing knowledge in the neurosciences tell us about these phenomena? Are there implications for treatment? Unfortunately, systematic information about treatment response in impulse control and other obsessive-compulsive spectrum disorders is limited, making potential differential pharmacological treatment response unavailable for scrutiny. This article will review the evidence from randomized, controlled trials of OCD treatment with paroxetine, a representative selective serotonin reuptake inhibitor (SSRI).

**Epidemiology**

Epidemiological studies report that the lifetime prevalence of OCD is between 2% and 3% in the general population. A cross-national study of OCD prevalence in the United States, Canada, Puerto Rico, Germany, Taiwan, Korea, and New Zealand yielded similar results, with prevalence rates ranging from 0.7% to 2.5%. It is estimated that between 4 and 6 million people in the US have OCD. The onset of symptoms occurs by adolescence in half the patients, with chronic symptoms usually lasting into adulthood. Comparable epidemiological information of impulse control and other obsessive-compulsive spectrum disorders is largely unknown, which is partly the result of their poor definition in our nomenclature.

OCD is frequently associated with comorbid psychiatric disorders. The most common comorbidity is major depression, occurring concurrently in 30% of patients (lifetime prevalence, 67%). Other common comorbidities...
are anxiety disorders, such as phobias, social anxiety disorder, and panic disorder; impulse control disorders, such as eating disorders and alcohol abuse; and neuropsychiatric disorders, such as Tourette’s syndrome. The optimal goal of treatment is to achieve symptomatic remission and functional recovery of both OCD and comorbid disorders.

**FUNCTIONAL ANATOMY OF OCD**

Advances in brain imaging have provided a window into the structure and functioning of the human brain, making it possible to examine neural regions and circuits relevant to the pathophysiology of OCD and the larger spectrum of disorders that share similar component characteristics. The core pathology appears to involve a cortico-basal ganglial-thalamo-cortical reverberating circuit. Specifically, the orbital prefrontal cortex and its subcortical connections are hyperactive, potentially the result of a disparity between direct and indirect striato-pallidal activity. Morphological studies suggest structural abnormalities in the caudate, thalamus, as well as the right frontal neocortex. A subgroup of childhood-onset OCD may be the consequence of molecular mimicry resulting from post-streptococcal immune reactions that damage basal ganglia structures. The functional consequences are impairment in the nonconscious (implicit) systems for learning mediated through the basal ganglia, and consequent recruitment of explicit memory systems involving medial temporal lobe structures to counteract the deficit.

The studies of neurocircuitry in pathological anxiety have focused on the amygdala as a critical node for fear conditioning and its close relationship with the hippocampus for contextual conditioning through explicit memory systems. Medial prefrontal cortical-amygdala circuits appear to mediate avoidance and its extinction. Functional brain-imaging studies in OCD appear to focus less on the amygdala, arguing against the primacy of anxiety in OCD.

One factor that may have contributed to some of the confusion in phenomenology and challenges in classification may be that a pathological insult does not necessarily limit itself to a specific or a single segregated neurocircuit. Thus, involvement of additional neurocircuits mediating motor function underlie tics seen in comorbid Tourette's syndrome.

**PHARMACOLOGICAL TREATMENT OPTIONS**

The tricyclic antidepressant clomipramine was the first medication consistently demonstrating efficacy in OCD, but adverse events from its anticholinergic and antiadrenergic properties limited patient use. With their tolerability and safety in overdose, the SSRIs became the treatments of choice for OCD. Several randomized, controlled trials have demonstrated the efficacy of the SSRIs to placebo or other medications.
The common outcome measure assessing efficacy in pharmacological trials in OCD is the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Response has been previously defined as a 25% to 35% reduction from baseline in the total Y-BOCS scores. Only recently have the remission criteria been defined. Ballenger\textsuperscript{25} proposed remission in OCD as a score of $\leq 8$ on the Y-BOCS, with the Hamilton Rating Scale for Anxiety (HAM-A) total score of $\leq 10$ indicating minimal anxiety, the Hamilton Rating Scale for Depression (HAM-D) total score $\leq 7$ indicating minimal depressive symptoms, and mild or no disability on the Sheehan Disability Scale (SDS).

**Paroxetine Treatment of OCD**

The use of paroxetine in the short-term treatment of OCD was evaluated in 2 randomized, placebo-controlled, double-blind trials of 12 weeks’ duration.\textsuperscript{24,26} One long-term maintenance trial lasted 1 year.\textsuperscript{27,28} The primary outcome measures used to assess efficacy were Y-BOCS scores\textsuperscript{24,26} and the National Institute of Mental Health Obsessive-Compulsive (NIMH-OC) scale.\textsuperscript{24}

Zohar and colleagues\textsuperscript{24} reported a multinational, randomized, double-blind, flexible-dose trial of paroxetine compared with clomipramine and placebo in 406 patients. Patients were randomized to receive paroxetine 20 to 60 mg (N=198), clomipramine 50 to 250 mg (N=94), or placebo (N=99) for 12 weeks. Doses were adjusted based on efficacy and adverse events. After 6 weeks, the reduction in the Y-BOCS score was significantly greater with both paroxetine and clomipramine when compared with placebo ($P<.05$). Reductions in the Y-BOCS scores for paroxetine and clomipramine continued to decrease during the 12-week period of the study and, compared with placebo, were statistically significant at week 12 (mean Y-BOCS scores, 18.8 for paroxetine, 17.8 for clomipramine, and 22.4 for placebo) (Figure 1). The most commonly received dose was 60 mg for paroxetine-treated patients (53% of patients) and 250 mg for clomipramine-treated patients (30%). Paroxetine was better tolerated, with 16% of the patients reporting adverse events compared with 28% of the patients treated with clomipramine ($P<.05$).

In another study, 348 patients with OCD were randomized to placebo (N=89), paroxetine 20 mg (N=88), paroxetine 40 mg (N=86), or paroxetine 60 mg (N=85) for 12 weeks.\textsuperscript{26} Beginning at week 4, patients treated with paroxetine 40 mg or 60 mg demonstrated statistically significant improvement from baseline on the Y-BOCS, and continued to improve at week 12 ($P<.017$). Paroxetine 20 mg did not separate from placebo on any efficacy parameters. Statistically significant differences between patients treated with 60 mg of paroxetine versus those treated...
with 20 mg of paroxetine were apparent ($P<.017$). The adverse-event profile, even with the higher doses, was similar to that seen in trials that used lower doses of paroxetine in the treatment of major depression.

The 257 patients who successfully completed the 12-week fixed-dose study of paroxetine versus placebo were enrolled in a 6-month, open-label, continuation trial to assess the degree of sustained clinical response to paroxetine. The mean Y-BOCS score decreased from 25.5 at pretreatment baseline to 19.8 after 12 weeks and to 14.6 after 6 months of open-label paroxetine treatment. The risk for relapse was 2.7 times greater among placebo-treated patients versus those receiving paroxetine during the 6 months of continuation treatment.

In the maintenance treatment component of the study, patients who met the criteria for a therapeutic response in the 6-month, open-label, continuation trial were then randomized in a double-blind manner to maintenance treatment with paroxetine (N=53) or placebo (N=51). The percent of patients who relapsed was significantly greater in the placebo group (59%) than in the paroxetine group (38%) ($P=.033$). The mean time to relapse after 12 months for paroxetine was 62.9 days versus 28.5 days for placebo. Long-term treatment with paroxetine was effective in maintaining therapeutic response and for preventing relapse for up to 1 year.

**FIGURE 1**

**Efficacy of Paroxetine and Clomipramine in the Treatment of Obsessive-Compulsive Disorder (OCD)**

- **Paroxetine (n=198)**
- **Clomipramine (n=94)**
- **Placebo (n=99)**

<table>
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<th>Week</th>
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<th>6</th>
<th>12</th>
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<td>Y-BOCS Score</td>
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<td>24.7</td>
<td>26.3</td>
</tr>
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<td></td>
<td>20.8</td>
<td>19.3</td>
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<td></td>
<td>18.8</td>
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* $P<.05$ vs placebo.

Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

Adapted with permission.  
Comparable efficacy of SSRIs has been reported in a meta-analysis. A 10-week study directly compared paroxetine, fluvoxamine, and citalopram in 30 adults with OCD. Analyses of the primary efficacy endpoints, the Y-BOCS, NIMH-OC, the Clinical Global Impressions (CGI), and the HAM-D, were performed under blinded conditions and showed no significant differences between the 3 treatments. However, the power to detect significant differences was seriously compromised by the small number of subjects studied.

A double-blind, placebo-controlled study of more than 300 children and adolescents with OCD demonstrated that paroxetine in doses ranging from 10 to 60 mg was effective in the treatment of pediatric OCD.

**NEUROIMAGING STUDIES OF PAROXETINE**

What does the pharmacological response of OCD to SSRIs such as paroxetine imply? Gilbert et al report that thalamic volume increases subsided to normal control levels with paroxetine treatment in a pediatric OCD sample. A study using single-voxel proton magnetic resonance spectroscopy in pediatric OCD found significantly greater glutamatergic concentrations in the caudate compared with healthy controls. Paroxetine treatment was associated with a decline in glutamatergic concentrations to the level in controls.

However, SSRI treatment has multiple neurochemical effects. Therefore, it is difficult to attribute improvement to a single pharmacological effect. The SSRIs may directly affect the balance of activity in the direct and indirect orbito-subcortical pathways. Additionally, the SSRIs may buffer the reactivity of fear circuits involving the amygdala and thus indirectly bring symptom relief. Additional effects of SSRIs include beneficial effects on neuropeptides such as the brain-derived neurotrophic factor (BDNF), enhanced neurogenesis, effects on corticotropin-releasing factor (CRF) neurons, glucocorticoid receptors, neurosteroids, and immune effects.

**DISCUSSION**

Like the other SSRIs, paroxetine has been studied in the short-term management of OCD in children, adolescents, and adults. Additionally, the benefits of paroxetine are maintained longitudinally. A direct comparison with clomipramine suggests equivalent efficacy of paroxetine in OCD, with more favorable adverse-event and safety profiles for paroxetine.

Compared with patients with major depression, those with OCD often require a longer period of treatment before clinical response is achieved. An adequate trial of an SSRI in OCD consists of at least 10 to 12 weeks of continuous treatment at the maximally tolerated dose.
initial response can take up to 8 weeks, and a plateauing of the benefits may require as much as 20 weeks, if not longer.\textsuperscript{19} The optimal doses of SSRIs for patients with OCD are often higher than those for other anxiety disorders or major depression. Targeted daily doses recommended for the treatment of OCD are clomipramine 250 mg, paroxetine and fluoxetine 60 mg, fluvoxamine 300 mg, and sertraline 100 to 200 mg.\textsuperscript{19} Patients who fail treatment with one SSRI are candidates for a trial with another SSRI. Twenty percent of patients who fail to respond to one SSRI will respond to a second agent.\textsuperscript{33} Between 40% and 60% of patients with OCD do not respond to SSRI treatment.

The proportion of patients achieving remission is rarely reported and may be in the range of 10% to 20% in acute (10- to 12-week) studies. This is considerably below the range reported with short-term pharmacological trials in other anxiety disorders and major depression.

Fully remitted patients on long-term therapy (ie, 1-2 years) may be candidates for discontinuation. Treatment with the SSRIs should be tapered gradually (ie, a 25% decrease in dosage every 2 months).\textsuperscript{34} However, relapse of OCD occurs in 65% to 95% of patients who discontinue SSRI therapy. Cognitive behavioral therapy using exposure and response prevention can enhance durability of response and prevention of relapse, particularly when pharmacological treatment is discontinued.\textsuperscript{35} But even with cognitive behavioral therapy, pharmacological treatment may be required indefinitely for the majority of OCD patients.\textsuperscript{33}

**DISCLOSURE**

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**REFERENCES**

PAROXETINE IN THE TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER