Pharmacological treatment for obsessive–compulsive disorder

Naomi A Fineberg

The systematic investigation of obsessive–compulsive disorder (OCD) has depended on the introduction of universally accepted diagnostic criteria and comprehensive rating scales that are sensitive enough to measure small treatment-related changes, such as the Yale-Brown Obsessive Compulsive Scale (YBOCS) (Goodman et al., 1989). This contribution reviews the key clinical questions relating to pharmacotherapy for OCD (Figure 1).

After 25 years of intensive pharmacological investigation, it still appears to be the case that OCD responds selectively to drugs that act as powerful inhibitors of the synaptic reuptake of serotonin—clomipramine and the selective serotonin reuptake inhibitors (SSRIs). Drugs lacking potent serotonin reuptake inhibitor (SRI) actions, such as the tricyclic antidepressants amitriptyline, nortriptyline and desipramine, and the monoamine oxidase inhibitors (MAOIs) clorgyline and phenelzine, have not been found to be effective in controlled studies. Nor is there convincing evidence supporting the efficacy of antipsychotics, benzodiazepines, lithium or electroconvulsive therapy (ECT) (Figure 2). The selectivity of the pharmacological response has generated hypotheses concerning the role of serotonin in the pathophysiology of the disorder but, so far, no unifying theory has emerged.

Key clinical questions for OCD pharmacotherapy

- What drug?
- What daily dose?
- How long should treatment continue?
- What are the long-term advantages/disadvantages?
- What happens when treatment is discontinued?
- What if the patient fails to respond?

Practice points

- Effective psychological treatment of OCD requires attention to both cognitive and behavioural aspects
- For some OCD patients, normalization and advice to cease neutralizing may be sufficient, but most require skilled treatment
- 'Normalizing' intrusions is important in reducing anxiety, as patients fear that their intrusions mean that they are bad or mad
- Relapse rate after treatment stops is very much lower in psychological treatment compared with pharmacological treatment

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Pharmacological specificity of OCD treatment

Effective
• Potent SRIs such as clomipramine, fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram

Ineffective
• Tricyclics (apart from clomipramine)
• MAOIs
• Lithium
• Antipsychotics
• Benzodiazepines
• ECT

1Have a possible adjunctive role, augmenting SRIs

Clomipramine – the earliest treatment

Promising reports from uncontrolled case studies performed in the 1970s were investigated in a large series of double-blind placebo-controlled trials that demonstrated conclusive evidence of efficacy for clomipramine in patients suffering with OCD. Some studies specifically excluded comorbid depression, while others demonstrated efficacy for clomipramine in patients with varying amounts of comorbid depression. Later studies confirmed that clomipramine was also effective in childhood and adolescent OCD, and focused attention on the importance of early recognition and treatment.

Two large, multicentre, placebo-controlled studies of clomipramine (in doses of up to 300 mg/day) in non-depressed adults showed a gradual, linear improvement in obsessions and compulsions, starting after only 1 week of treatment and continuing to the 10-week endpoint of the study (reviewed in Zohar and Fineberg, 2001). The resulting 40–50% improvement in baseline OCD ratings represented a substantial improvement in emotional and social well-being. This gradual improvement characterizes the anti-obsessional effect of SRI treatment (Figure 3), and distinguishes OCD from depression, where the clinical response occurs sooner. Extension studies have shown ongoing improvements for up to 2 years. For this reason, longer treatment periods of at least 12 weeks are advocated, and judgements concerning the degree of clinical response to a given drug should always take account of the duration of treatment.

SSRIs and the development of the therapeutic armamentarium

The demonstration in more recent studies that the more highly selective SSRIs are also effective, and show a similar slow, incremental treatment effect, suggests their anti-obsessional properties are related to the inhibition of neuronal reuptake of serotonin in the central nervous system (CNS). Convincing evidence from large-scale, placebo-controlled studies supports the efficacy of fluvoxamine, fluoxetine, sertraline, paroxetine and citalopram in the acute treatment of OCD (reviewed in Zohar and Fineberg, 2001). There is little doubt that SRIs are effective in patients with significant levels of concurrent depression. The improvement in depressive symptoms occurs in parallel with improvements in the OCD, and the presence of moderate levels of comorbid depression does not interfere with the treatment response. The relative strength of the anti-obsessional effect of drug treatment is highlighted by the observation that SRIs still show superiority compared with placebo in studies where there has been concurrent administration of exposure therapy in the placebo-treated group.

The development of SSRIs as treatments for OCD has been an important advance, in view of their improved safety and tolerability compared with clomipramine. Yet in approximately 30% of patients the clinical response to drugs is disappointing, and better treatments would be welcome.

What is the most effective dose of SRI?

OCD has traditionally been thought to require higher doses of medication than depression and anxiety. In order to examine this, head-to-head studies are needed to compare different fixed doses of the active drug with placebo. (Clomipramine has not been examined in this way.) Whereas single-dose studies showed efficacy for relatively low fixed daily doses of clomipramine (75 mg and 125 mg) compared with placebo, most studies used flexible doses titrated toward the upper end of the range (200–300 mg/day).

Similarly, fluvoxamine was found to be effective in doses ranging from 150 mg/day to 300 mg/day.

Fluoxetine, paroxetine and sertraline have each been investigated using a series of multiple fixed doses. In the case of fluoxetine, all three fixed doses (20 mg, 40 mg and 60 mg/day) were found to be effective, but the greatest response was seen in the patients receiving the highest doses. A meta-analysis of the grouped data showed that the 60 mg dose was significantly more effective than 20 mg. Two fixed-dose comparisons of 20 mg, 40 mg and 60 mg of paroxetine produced similar findings. In both studies the 40 mg and 60 mg doses were effective, but the 20 mg dose did not separate from placebo (Dunbar et al., 1995; Hollander et al., 2003). Interestingly, in the fixed-dose study of sertraline the 50 mg and 200 mg doses were superior to placebo, whereas the 100 mg dose was not, but this study may have been underpowered.

The data have been interpreted to suggest that the highest dose levels tested in the studies (60 mg paroxetine, fluoxetine

The anti-obsessional profile of SRIs

• Early onset of response may be hard to detect
• Slow, incremental improvements over weeks and months
• Positive dose–response relationship (established for most compounds)
• Comprehensive improvement in obsessions, compulsions and mood
• Effects sustained as long as treatment continues
• Relapses prevented in long-term treatment
• Inadequate response in a significant minority of cases
and citalopram; 200 mg sertraline) are associated with better anti-obessional efficacy. Some psychiatrists use even higher doses of SSRIs, particularly in the treatment of resistant OCD, but in the absence of controlled data this practice cannot be recommended without reservation.

**Dose titration**

Improvements in OCD usually take several weeks to become established, irrespective of the dose, and it is helpful to warn patients about this from the outset. Unlike panic disorder, OCD is not usually associated with an exacerbation of anxiety in the first few days of treatment. Given that higher doses are associated with more adverse effects, it is recommended to start treatment at lower dose levels and, titrating against clinical response, slowly and steadily increase the dose over weeks and months. The clinician needs to strike a delicate balance between speed of response and tolerability.

OCD sufferers are notoriously poor at recognizing their own improvements, and it is useful to enlist the help of friends or relatives to inform on early signs of clinical improvement. The application of specific observer-rated scales (such as the YBOCS (Goodman et al., 1989) can help detect small improvements in the clinical setting.

A substantial proportion of patients show a delayed response, with improvements occurring only after several months. These cases are challenging, and there is often pressure to change treatments that have been shown to be effective in short-term studies maintain their efficacy over the longer term. Evidence for long-term efficacy can be derived from a variety of studies. Investigators have taken treatment responders from acute treatment studies and transferred them to uncontrolled treatment with an SSRI, with the result that the response has increased over time with no evidence of tolerance developing.

A small number of randomized, double-blind, placebo-controlled extension studies have actively followed up treatment responders from acute efficacy studies. Patients continued to improve for at least 1 year if they remained on the active treatment, whereas patients on placebo did not. Drop-out rates for SSRIs were markedly lower than for clomipramine. For example, in a double-blind continuation study of sertraline (Greist et al., 1995) only 13% of patients dropped out of treatment prematurely over the 40-week extension period. Of these, one-third blamed side-effects and two-thirds blamed unsatisfactory clinical response. The completers from this study were followed up for a further year on open-label sertraline and showed significant additional improvements in their OCD over the course of the second year, with a reduced incidence of side-effects compared with the earlier study.

It would appear that efficacy is sustained in the longer term, and patients continue to improve for at least 2 years (probably for longer) after the start of their treatment. With continued treatment, side-effects abate over time, adding to the therapeutic benefit. There are no controlled data on the best doses for long-term treatment, although the adage ‘the dose that gets you well, keeps you well’ probably applies. The results from a fixed-dose trial with fluoxetine support the 60 mg dose as being the most effective over a 24-week extension phase (Romano et al., 1998). Most experts recommend continuing treatment at the higher dose levels.

**Is pharmacological treatment effective in the longer term?**

OCD is a chronic illness and clinicians need to know whether treatments that have been shown to be effective in short-term studies maintain their efficacy over the longer term. Evidence for long-term efficacy can be derived from a variety of studies. Investigators have taken treatment responders from acute treatment studies and transferred them to uncontrolled treatment with an SSRI, with the result that the response has increased over time with no evidence of tolerance developing.

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**How long should pharmacotherapy continue?**

Once again, the evidence from controlled studies is helping to inform clinical practice. A small number of double-blind studies have evaluated whether prolonged SSRI treatment prevents relapse. Lack of agreed criteria for defining a relapse has bedevilled the interpretation of relapse-prevention studies in OCD.

In the double-blind study by Pato et al. (1988), 16 out of 18 patients who had shown sustained improvements on clomipramine showed a substantial worsening of their obsessive–compulsive symptoms within 4 weeks of randomization to placebo. The re-emergence of the OCD was gradual and progressive and was not related to the duration of clomipramine pre-treatment, which exceeded 2 years in some cases. In this study, reinstatement of the clomipramine resulted in improvement in all the patients to a level close to that achieved before the discontinuation, but other authors have reported less favourable results.

Two large studies investigated subjects who had responded to 6 months’ open-label paroxetine and showed that those who continued on the active drug suffered significantly fewer relapses over the following 6 months than those who were randomized to placebo. In the study by Dunbar et al. (1995), approximately 10% of the paroxetine-treated group showed a full relapse, compared with 18% on placebo. The clinical relevance of a partial relapse, as defined in this study, has been questioned since it may represent a transient fluctuation in symptoms rather than a sustained deterioration. YBOCS scores were maintained or slightly improved in the paroxetine group, but deteriorated in the placebo group.

The study by Hollander et al. (2003) produced strikingly similar findings: patients randomized to placebo showed a rapid and significant recurrence of their OCD within 2 weeks, while those who continued on paroxetine showed further improvement. Using a conservative criterion for relapse – defined as a return to baseline YBOCS scores – 9.4% of the paroxetine-treated patients relapsed over the 6-month follow-up, compared with 21.6% on placebo.

The study by Romano et al. (1998) showed a more favourable relapse rate (roughly 32% over the course of 12 months) following double-blind discontinuation of fluoxetine after 20 weeks’ active treatment. However, patients remaining on 60 mg fluoxetine still had significantly lower rates of relapse (17.5%) than those switched to placebo.

These data suggest that medication confers protection against relapse for as long as it is continued, and argue for the unlimited continuation of treatment, as long as patients can tolerate it. Discontinuation, if necessary, should be gradual to minimize discontinuation effects, and patients should be warned to look out for the early signs of relapse, whereupon reinstatement of the drug may achieve the same level of improvement as before, although this cannot be guaranteed.
SSRIs vs. clomipramine

Head-to-head studies are needed to test the relative efficacy and tolerability of different treatments, but no such studies have compared different SSRIs. At present, therefore, we must assume equivalent effectiveness for these compounds. The selection of a particular SSRI may take account of other factors, such as interactions with other drugs that the patient may be taking. In this respect, fluoxetine, paroxetine and, to a much lesser extent, sertraline inhibit the P450 isoenzyme CYP2D6, which metabolizes tricyclic antidepressants, antipsychotics and β-blockers. Fluvoxamine inhibits CYP1A2, which metabolizes warfarin, tricyclics, benzodiazepines and some anti-arrhythmics. Citalopram does not significantly affect hepatic metabolism. Fluoxetine has a long half-life and fewer discontinuation effects, which can be advantageous for patients who forget to take tablets.

Several studies have compared clomipramine with one or other SSRI, and on the whole the results have shown equivalent efficacy for clomipramine and paroxetine, fluvoxamine and fluoxetine. A study of sertraline found that it outperformed clomipramine on some measures, but the doses of clomipramine may have been too low to allow a fair comparison. Meta-analyses of existing studies, which suggested clinical superiority for clomipramine over the SSRIs, have been criticized for failing to take account of the important differences between the studies under examination.

Although the comparator studies suggest equivalent efficacy, the SSRIs are associated with a more favourable side-effect profile and are better tolerated than clomipramine. These factors assume paramount importance for OCD sufferers, who are expected to take treatment at high doses for unlimited periods.

Compared with clomipramine, which, in high doses, produces serious anticholinergic side-effects, a high risk of convulsions (up to 2%) and potentially dangerous cardiotoxicity, the SSRIs are much better tolerated, although they are responsible for more asthenia, insomnia and nausea. All SSRIs are associated with impaired sexual performance (30%) and some cause weight gain, but clomipramine appears to be more problematic than the SSRIs in this respect. Sexual function should be carefully monitored and, if necessary, strategies such as dose-reduction and short drug holidays can be considered if the patient is stable.

First-line treatment

The superior tolerability of SSRIs and the lower rate of premature discontinuation, relative to clomipramine, offer considerable benefits in the long-term management of OCD, and indicate that they should be considered the treatment of choice. Clomipramine should be reserved as a second-line treatment for patients who cannot tolerate SSRIs or have failed to respond to them.

Treatment strategies for incomplete response on SRIs

In approximately 30% of cases, residual symptoms remain in spite of prolonged treatment with SRI drugs. The problem of partial responders is an important area that has not yet received adequate controlled investigation. Uncontrolled reports suggest that increasing doses can produce a better effect, and intravenous clomipramine has been found to be effective in a single controlled experiment. Switching from one SSRI to another can sometimes be helpful (reviewed in Zohar and Fineberg, 2001). Combining clomipramine with an SSRI has been advocated by some experts, but pharmacokinetic interactions on the hepatic cytochrome P450 isoenzymes, leading to a build-up of clomipramine, can be dangerous. Plasma-level and ECG monitoring are advisable if this strategy is considered.

A variety of augmentation strategies may be preferred, since they are based on the results of randomized controlled trials (Figure 4). Two studies have shown that low doses of adjunctive risperidone (1–2 mg) improved responses to SSRIs in resistant patients without tics, and one study has shown efficacy for adjunctive quetiapine (<200 mg/day) in a similar population. The use of atypical antipsychotics in this area is very promising, but there have been case reports of clinical worsening associated with SRI–antipsychotic combinations, possibly related to higher doses of the antipsychotic. The use of standardized instruments to monitor clinical progress in this resistant group of patients is recommended.

Most benzodiazepines are ineffective, but clonazepam, which is thought to produce a more prominent serotonergic effect, was effective in combination with an SRI in a small controlled study, suggesting a possible role for this drug as an agent of augmentation. Clonazepam does not show anti-obsessional efficacy as monotherapy, though. Promising reports of the effect of augmenting SSRIs with buspirone have not stood up to scrutiny under controlled conditions. Nor is there evidence that augmentation with lithium has a role in OCD. ECT is generally unhelpful.

Double-blind, placebo-controlled pharmacotherapy studies in treatment-refractory OCD

Positive results suggesting efficacy

- Adding risperidone
- Adding quetiapine
- Adding haloperidol
- Intravenous clomipramine
- Adding clonazepam

Negative results suggesting lack of efficacy

- Adding lithium
- Adding buspirone
- Adding desipramine
- Adding tri-iodothyronine (liothyronine)
- Adding inositol

1Primarily in ‘tic-related’ OCD
2Investigational in many countries
3Small numbers and improvements not apparent on all OCD rating scales

REFERENCES

Most people will experience anxiety about health at some stage, perhaps after noticing a new or unexpected bodily symptom, in response to media coverage of a specific disease or following medical tests or physical illness. This is usually relatively short-lived, and anxiety subsides as symptoms abate or in response to reassurance from a doctor or other health professional. However, in some cases it persists and becomes a clinically significant problem.

‘Severe health anxiety’ refers to fears and beliefs that arise from misinterpreting bodily symptoms and health-related information as evidence of a potentially serious degenerative or life-threatening disease. Anxiety of this sort is rarely allayed for long by medical reassurance, and tends to shift from one symptom to another.

Severe health anxiety and hypochondriasis

Severe and persistent health anxiety is often diagnosed as hypochondriasis (using DSM-IV criteria, see Figure 1) or hypochondriacal disorder (ICD-10). These diagnostic constructs have been criticized (see Starcevic (2001) for a full discussion) and there is some debate over whether hypochondriasis should be classified as a somatoform disorder or as an anxiety disorder. Although somatic symptoms are prominent, hypochondriasis has phenomenological similarities with anxiety disorders, most notably the fear and threat interpretations.

Patients generally dislike the term hypochondriasis, viewing it as pejorative and suggestive of imaginary or factitious illness or malingering. It is probably more useful clinically to conceptualize hypochondriasis as severe and persistent health anxiety, at the far end of a continuum that has mild and transient health anxiety at its other end (Salkovskis and Warwick, 2001).

Clinical presentations of severe health anxiety

Severe health anxiety is characterized by pronounced disease conviction: sufferers believe that they have a serious, terminal or degenerative physical disease that doctors have failed to diagnose. Illness beliefs tend to fluctuate in severity, and periods of acute anxiety often alternate with phases of relative calm.