Pharmacological treatment for obsessive–compulsive disorder

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Abstract

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. This contribution reviews the key clinical questions relating to pharmacotherapy for OCD. After 30 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, nortyiptyline 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 benzodiazepines, lithium or electroconvulsive therapy (ECT). However, symptoms often respond only partially to SRIs and for around one-third of cases the response is poor. Increasing dosages or switching between SRIs are practical next steps. Growing evidence supports the efficacy of adding first- or second-generation antipsychotic agents, but long-term data are lacking.

Keywords antipsychotic drugs; obsessive–compulsive disorder; OCD; pharmacotherapy; randomized controlled trials; serotonin reuptake inhibitors

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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).[1] This contribution reviews the key clinical questions relating to pharmacotherapy for OCD (Table 1).

After 30 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 benzodiazepines, lithium or electroconvulsive therapy (ECT) (Table 2). However, symptoms often respond only partially to SRIs and for around one-third of cases the response is poor. Increasing dosages or switching between SRIs are practical next steps. Growing evidence supports the efficacy of adding first- or second-generation antipsychotic agents, but long-term data is lacking.

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.[2–7] Later studies confirmed that clomipramine was also effective in childhood and adolescent OCD, and focused attention on the importance of early recognition and treatment.[8]

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[9]). The resulting 40–50% improvement in baseline OCD ratings represented a substantial improvement in emotional and social wellbeing. This gradual improvement characterizes the anti-obsessional effect of SRI treatment (Table 3) and distinguishes OCD from depression, where the clinical response occurs sooner. Extension studies have shown ongoing improvements for

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?

Table 1

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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[a]
- Benzodiazepines
- Oxytocin
- Naloxone
- ECT

[a]Have a possible adjunctive role, augmenting SRIs.

Table 2

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, showing a similar slow, incremental treatment effect, suggests that 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, escitalopram and citalopram in the acute treatment of OCD (reviewed in Fineberg and Craig, 2006[10]). 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.[11]

There are few alternatives to SRIs in the treatment of OCD. Studies of venlafaxine, which is predominantly serotonergic at lower doses, have not consistently demonstrated an anti-obsessional effect.[12]

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.

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

Table 3

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,[13] 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.[14]

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.[15,16] 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 and citalopram; 200 mg sertraline) are associated with better anti-obsessional 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. The arguments for slower dose increases are particularly persuasive for children and the elderly. Special care with higher doses is also required for cases

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