

# Evidence-based pharmacotherapy for obsessive–compulsive disorder

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The development of effective pharmacotherapy has revolutionised the treatment of obsessive–compulsive disorder (OCD), and has generated an explosion of interest in this previously poorly understood area of psychiatry. Once considered a rare, refractory form of learnt behaviour, we now recognise OCD to be a common, treatable illness, with a distinctive pathophysiology and pharmacology. Wide-ranging epidemiological surveys have demonstrated a surprisingly high lifetime prevalence amounting to 2–3% of the general population worldwide (Robins *et al*, 1984). Yet only a fraction of sufferers come forward for treatment and often the diagnosis is missed.

Obsessive–compulsive disorder appears somewhat, but not markedly, more common in women than men (gender ratio 1.5:1). The mean age of onset has been reported as 20 years, with bimodal peaks at 12–14 years and 20–22 years. There is a high incidence in childhood, and, if left untreated, the illness runs a fluctuating, unremitting course, with the greatest prevalence occurring in early–middle adult life. A substantial comorbidity with a variety of DSM–IV (American Psychiatric Association, 1994) Axis I and II disorders – most notably with depression – and increased rates of suicidal behaviour have been identified. The costs of OCD to society in terms of individual suffering, diminished human potential and lost revenue are acknowledged to be high.

The systematic investigation of OCD has depended, to a large extent, on the introduction of universally accepted diagnostic criteria (see Box 1) and the development of comprehensive rating scales that are sensitive enough to measure small treatment-related changes across the whole range of symptoms, such as the six- and eight-item scales (respectively, Montgomery & Montgomery 1980; Thoren *et al*, 1980)

derived from the Comprehensive Psychopathological Rating Scale (Asberg *et al*, 1978) and the more recent Yale Brown Obsessive Compulsive Scale (YBOCS; Goodman *et al*, 1984).

In spite of scientific advances, OCD remains poorly recognised and undertreated by the medical

**Box 1. ICD–10 criteria for obsessive–compulsive disorder (adapted from World Health Organization, 1992)**

Either obsessions or compulsions (or both) present for most days for at least two weeks

*Obsessions and compulsions share the following features, all of which must be present*

Acknowledged as originating in the patient's mind, not imposed from outside

Repetitive and unpleasant. At least one acknowledged as excessive or unreasonable

At least one obsession or compulsion unsuccessfully resisted (but if symptoms are long-standing, resistance may be minimal)

The obsession or compulsion is not intrinsically pleasurable

Obsessions or compulsions cause distress or interfere with social functioning or lifestyle, often by wasting time

Exclusion criteria: not due to other mental disorders such as schizophrenia and related disorders or mood disorders

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profession. The average time lag between the onset of symptoms and the initiation of effective treatment has been estimated recently at between 7 and 17 years. It is often only when depression supervenes, as occurs in two-thirds of cases at some point in their illness, that OCD sufferers come forward for treatment. At this point, it is important that the OCD is not missed since the success of the clinical intervention will depend, to a large extent, on the effective treatment of the OCD (Box 2).

## OCD and the serotonin hypothesis

After two decades of intensive pharmacological investigation, it still appears that OCD responds selectively to drugs that act as powerful inhibitors of the synaptic reuptake of serotonin – that is, clomipramine and the selective serotonin reuptake inhibitors (SSRIs). Drugs lacking potent serotonin reuptake inhibitor actions – such as the conventional tricyclics amitriptyline, nortriptyline and desipramine, and the monoamine oxidase inhibitors clorgyline and phenelzine (Jenike *et al*, 1997) – 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) (reviewed in Montgomery *et al*, 1990)(Box 3). 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. It is now widely believed that OCD encompasses a heterogeneous group of illnesses, and that neurotransmitters other than serotonin play important roles in the aetiology

### Box 2. Key questions for OCD pharmacotherapy

What kind of drug?  
 What dose?  
 How long should treatment continue?  
 What are the long-term advantages/disadvantages?  
 What happens if treatment is discontinued?  
 What if the patient fails to respond?  
 Are non-pharmacological strategies appropriate?

of the disorder. Alterations in neurotransmission between the orbitofrontal cortex and the corpus striatum have been postulated, and research is currently broadening to explore possible abnormalities in dopamine, noradrenaline, neuropeptide and immunological functioning. SSRIs may act by promoting intrinsic, serotonergic, neuropsychological defence mechanisms, rather than by reversing a key pathophysiological abnormality (Fineberg *et al*, 1997).

## Clomipramine – the earliest effective treatment

Early, promising reports from uncontrolled case studies performed in the 1970s were actively investigated in a large series of double-blind placebo-controlled trials that demonstrated conclusive evidence of efficacy for clomipramine in patients suffering with OCD (reviewed in Fineberg *et al*, 1992). The seminal study by Montgomery (1980) specifically excluded patients suffering with comorbid depression and showed efficacy for a relatively low fixed daily dose (75 mg) in a small, carefully selected group of individuals. In the same year, other studies demonstrated efficacy for clomipramine in patients with varying amounts of comorbid depression. Later studies confirmed that the drug was also effective in childhood and

### Box 3. Pharmacological specificity of obsessive-compulsive disorder

#### *Effective as monotherapy*

Potent serotonin reuptake inhibitors such as clomipramine, fluvoxamine, fluoxetine, paroxetine, sertraline

#### *Ineffective as monotherapy*

Tricyclics (apart from clomipramine)  
 Monoamine oxidase inhibitors  
 Lithium  
 Antipsychotics<sup>1</sup>  
 Benzodiazepines<sup>1</sup>  
 Electroconvulsive therapy

1. Possible adjunctive role, augmenting serotonin reuptake inhibitor monotherapy, for conventional antipsychotics and clonazepam

adolescent OCD, and focused attention on the importance of early recognition and treatment.

### *Response to medication*

The early clomipramine studies were small by current standards and yet in spite of this, superiority over placebo was easily demonstrated, with significant drug–placebo differences emerging after only one or two weeks of active treatment. The success of these studies reflected the special qualities of the patients under investigation at that time. Most had a long history of stable, severe untreated illness, and the proportion of treatment-refractory cases was small.

Two large multi-centre placebo-controlled studies of clomipramine (up to 300 mg/day) in non-depressed adults replicated Montgomery's (1980) finding, and showed a slow, gradual, linear improvement in obsessions and compulsions, starting after only one week of treatment and continuing to the 10-week end-point of the study. The resulting 40–50% improvement in baseline obsessive–compulsive ratings over the 10-week acute treatment period represented a substantial improvement in emotional and social well-being – bearing in mind that a reduction of only one or two points (out of a maximum of 40) on the YBOCS is associated with a reduction of several hours a day in time spent ritualising. In contrast, the improvement in the placebo-treated groups was consistently lower than 10%.

This slow, gradual improvement characterises the anti-obsessional effect of serotonin reuptake inhibitor treatment (Box 4) and distinguishes OCD from depression, where the clinical response occurs sooner. Extension studies have shown ongoing improvements for up to two years. For this reason, longer trial treatment periods of 10–12 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**

Clomipramine is a powerful serotonin reuptake inhibitor, but it has an active metabolite with strong noradrenergic properties. The demonstration in more recent studies that the more highly selective SSRIs are also effective, and show a similar slow, incremental treatment effect, points to their anti-obsessional actions being related to this pharmacological property.

#### Box 4. Characteristics of the anti-obsessional response on serotonin reuptake inhibitors

Early onset of response may be hard to detect  
Slow, incremental improvements over weeks and months  
Minimal placebo effect  
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

Convincing evidence from large-scale placebo-controlled studies supports the efficacy of fluvoxamine, fluoxetine, sertraline and paroxetine in the acute treatment of OCD (reviewed in Montgomery, 1998). Open reports hinting at efficacy for citalopram still await confirmation in controlled studies.

In contrast to exposure therapy, serotonin reuptake inhibitors are equally effective at relieving obsessional thoughts and compulsive rituals, whereas compulsions are more amenable to behavioural treatment than obsessions are. The relative strength of the anti-obsessional effect of drug treatment is highlighted by the observation that serotonin reuptake inhibitors still show superiority compared with placebo in studies where there has been concomitant 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 roughly 30% of patients, the clinical response to drugs is disappointing, and better treatments would be welcome (see below).

### *Serotonin reuptake inhibitors and comorbid depression*

There is little doubt that serotonin reuptake inhibitors 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 comorbid depression does not appear to interfere with the treatment response.

Some early studies were criticised for the inclusion of patients with significant levels of depression that theoretically could have confounded the results. In the light of this criticism, the more recent studies tended to exclude patients with comorbid depression in order to be sure that the drug was acting primarily on the OCD. However, a small number have looked specifically at obsessional patients with depression. Clomipramine, fluvoxamine and sertraline have all been compared with the noradrenergic antidepressant desipramine in groups of patients in whom comorbid depression was allowed (Goodman *et al*, 1990). In the sertraline study, patients were specifically selected for the presence of significant depression. In each case, the serotonin reuptake inhibitor was superior to desipramine, which was ineffective on both the obsessional and depressive symptoms.

It is unusual for an antidepressant like desipramine to show such a poor response. These results suggest that the depression is either integral or secondary to the OCD, and imply that depressed patients with OCD should be treated with a serotonin reuptake inhibitor. For this reason, clinicians should screen patients presenting with affective symptoms for the presence of OCD.

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## Changes in study populations

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The success of clomipramine and the SSRIs has led to their rapid acceptance as first-line treatments, and it has become increasingly difficult for the specialist research centres to find patients who are not already receiving this form of treatment. This has compromised the recruitment of treatment-naïve patients to the more recent studies, where greater numbers of treatment-refractory individuals have been included. Accordingly, the magnitude of the observed treatment effect has diminished from a 40–50% average reduction in baseline scores in the clomipramine studies, to around 30% in the later studies looking at SSRIs, and only 50% SSRI-treated cases showed a clinically meaningful improvement using recognised criteria for clinical response (Wood *et al*, 1993). The response rates seen in general psychiatric clinics are probably closer to the original clomipramine study data.

Increased placebo response rates, in some cases exceeding 20% improvement in baseline scores and 30% 'responder rates', have also been observed in the more recent studies, resulting from the inclusion of milder, atypical cases, some of whom undergo spontaneous remissions. The rise in the placebo response rate strengthens the argument against drawing conclusions about efficacy from open,

naturalistic reporting, and emphasises the importance of controlled investigation.

The net effect of these changes has been to reduce the statistical power of the studies, so that larger numbers are now needed to test the efficacy of new treatments. Meta-analyses of existing studies are increasingly attractive, but if they fail to take these changes into account, they are likely to be misleading.

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## What is the most effective dose?

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Obsessive-compulsive disorder has traditionally been thought to require higher doses of medication than depression and anxiety. In order to examine this question we need head-to-head studies comparing 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 towards the upper end of the range (200–300 mg/day). Similarly, fluvoxamine was found to be effective in doses of 150–300mg/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, 40 and 60 mg/day) were found to be effective, but the greatest response was seen in the patients receiving the highest dose, and a meta-analysis of the grouped data showed that the 60 mg dose was significantly more effective than 20 mg. A multiple fixed dose comparison of 20, 40 and 60 mg paroxetine produced similar findings. In this study the 40 and 60 mg doses were effective, but the 20 mg dose was no different from placebo (reviewed in Fineberg *et al*, 1994). Interestingly, in the multiple fixed dose study of sertraline (Greist *et al*, 1995), 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. A smaller study (Ushijima *et al*, 1997) showed signs suggesting that a dose-response relationship exists for sertraline as well.

These results 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.

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## Dose titration

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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 days of treatment. In view of the fact that the higher doses are associated with an increased frequency of adverse effects, it is recommended to start treatment at lower dose levels and, titrating against clinical response, to slowly and steadily work the dose upwards over weeks and months. The clinician needs to strike a delicate balance between speed of response and tolerability.

Sufferers with OCD are notoriously poor at recognising their own improvements and it is useful, where possible, to enlist the help of friends or relatives to inform on early signs of clinical improvement. The application of specific observer-rated scales can be of additional benefit in detecting small improvements in the clinical setting.

A substantial proportion of patients, perhaps up to 20%, show a delayed response, with improvements occurring only after several months. These cases can be extremely challenging for the clinician, and there is often pressure to change treatments or escalate the doses prematurely. As a general rule, it is best to wait at least three months to allow the treatment effect time to develop – in some cases, even longer periods are required.

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## Is pharmacotherapy effective in the longer-term?

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Obsessive–compulsive disorder is a long-term illness and we need to know whether treatments that have been shown to be effective in short-term studies maintain their efficacy over the longer term.

In comparison to the large amount of evidence supporting the efficacy of serotonin reuptake inhibitor drugs in the acute treatment of OCD, the long-term outcome has been little studied and remains poorly understood.

Evidence for long-term efficacy can be derived from a variety of sources. Cottraux *et al* (1990) reported ongoing superiority for fluvoxamine over placebo after six months of double-blind treatment. Other investigators have taken ‘treatment responders’ from acute treatment studies and have transferred them to open treatment with an SSRI,

with the result that the response has increased over time with no evidence of tolerance developing.

A small number of double-blind placebo-controlled extension studies have actively followed-up treatment responders from acute efficacy studies. Patients continued to improve for at least one year if they remained on the active treatment, whereas patients on placebo did not. Drop-out rates were markedly lower for SSRI than for clomipramine. For example, in the 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. Those who completed this study were followed-up for a further year on open-label sertraline, and showed significant additional improvements in their OCD symptoms over the course of the second year, with a reduced incidence of side-effects compared with the earlier study.

It would appear, therefore, that efficacy is sustained in the longer term, and patients will continue to improve for at least two years (probably for longer) after the start of their treatment. With continued treatment, side-effects abate over time, adding to the therapeutic benefit.

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## What is the best dose for long-term treatment?

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There is still no published controlled data informing on the best doses for long-term treatment, although the adage ‘the dose that gets you well, keeps you well’ probably applies. Preliminary data looking at fixed dose treatment with fluoxetine supports the 60 mg dose as being the most effective over a 24-week extension phase (Romano *et al*, 1998). There is little evidence supporting the reduction of doses in the longer term, apart from one small study where lowering the dose of clomipramine and fluvoxamine did not appear to increase relapse rates (Mundo *et al*, 1997). Most experts recommend continuing treatment at the higher dose levels. In this respect, current UK licensing restrictions applying to sertraline in doses of 150 mg or more are unhelpful.

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## How long should treatment continue?

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Here again, there is insufficient evidence from controlled studies to inform clinical practice. A small number of double-blind discontinuation studies have been performed, but it has been difficult to disentangle ‘discontinuation effects’ resulting from the abrupt discontinuation of the medication from

the re-emergence of the underlying illness. Discontinuation effects are related to the pharmacological properties of the compound and are believed to complicate paroxetine and clomipramine rather more than fluoxetine.

In the discontinuation 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 four weeks of crossing-over to placebo. The re-emergence of the symptoms was gradual and progressive and was not related to the duration of clomipramine pre-treatment, which exceeded two years in some cases. In this study, reinstatement of the clomipramine resulted in improvement in all the patients to a level close to the improvements achieved before the discontinuation, but other authors have reported less favourable results.

A larger-scale, longer discontinuation study investigated subjects who had responded to six months' paroxetine treatment and showed that those who continued on the active drug suffered significantly fewer relapses over the course of the following six months than those who were switched to placebo. In the paroxetine-treated group, roughly 10% showed a full relapse, in comparison to 18% on placebo. However, a partial relapse occurred in almost 40% of the patients on paroxetine and 60% 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 (Dunbar *et al*, 1995).

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 showed significantly lower rates of relapse (17.5%) than those switched to placebo, and there were no differences in adverse effects reported by those on long-term fluoxetine or placebo.

These data suggest that medication confers protection against relapse as long as the medication is continued, and support the unlimited continuation of treatment as long as patients can tolerate it. Discontinuation, if necessary, should be gradual to minimise 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.

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## SSRIs – equally efficacious and better tolerated than clomipramine

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There is no single 'gold-standard' treatment for OCD. Head-to-head studies are needed to test the relative efficacy and tolerability of different treatments, and no such studies have compared different SSRIs. For the present, therefore, we must assume equivalent effectiveness for these compounds. The selection of a particular agent for a patient may need to take account of other factors, such as possible 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 CYP 2D6 which metabolises tricyclic antidepressants, antipsychotics, anti-arrhythmics and beta-blockers, whereas fluvoxamine mainly inhibits CYP 1A2 and interacts with warfarin, tricyclics, benzodiazepines and some anti-arrhythmics. Fluoxetine has a long half-life and fewer discontinuation effects, which can be advantageous for patients who forget to take their 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 this drug outperformed clomipramine on some measures, however the doses of clomipramine may have been too low to allow a fair comparison (Bisserbe *et al*, 1997). Another small study showed an advantage of clomipramine over fluoxetine. A small number of meta-analyses of existing studies which suggested clinical superiority for clomipramine over the SSRIs have been criticised for failing to take account of important differences between the studies under examination (reviewed in Montgomery, 1998).

Although the comparator studies suggest equivalent efficacy, there is clear evidence that the SSRIs are associated with a more favourable side-effect profile and are better tolerated than clomipramine (Bisserbe *et al*, 1997). In the comparator studies, the drop-out rate from adverse effects on clomipramine (around 17%) was consistently higher than that for the SSRIs (around 9%). These factors assume paramount importance for OCD sufferers, who are expected to take treatment at high dose levels for unlimited periods. Compared to 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

serotonin reuptake inhibitors are associated with impaired sexual performance (30%) and some cause weight gain, but clomipramine appears more problematic than the SSRIs in this respect. Interestingly, unlike people with depression, OCD sufferers appear to tolerate the nausea reasonably well, but weight gain can be problematic (Rasmussen *et al.*, 1994). 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.

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 the SSRIs should be considered the treatments of choice with clomipramine reserved as a second-line treatment for those who cannot tolerate or who have failed to respond to them.

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## Treatment strategies for partial responders

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Although most patients experience substantial improvements, for many, the treatment response is not complete. In roughly 30% of cases, in spite of prolonged treatment with serotonin reuptake inhibitor drugs, troublesome, residual symptoms remain. The problem of partial responders is an important area that has not yet received adequate controlled investigation.

Factor analysis of study data suggests that those patients who had only been treated previously with behaviour therapy and not with drugs, those with more severe OCD and those with high or low levels of comorbid depression showed better responses to medication. Patients with comorbid tics and personality disorders showed a less favourable response.

A number of strategies can be considered for treating partial responders. Clinical experience suggests that it is appropriate to persist with serotonin reuptake inhibitor treatment even in patients who show little sign of improvement, since a delayed response may occur after six months or more. Controlled studies are needed to examine whether or not this represents a specific pharmacological effect.

Uncontrolled reports suggest that, for some patients, increasing doses can procure a better effect. In others, switching from one SSRI to another can sometimes be helpful. Combining clomipramine with an SSRI has little to recommend it, and plasma-level monitoring is advisable, since the

pharmacokinetic interactions on the hepatic cytochrome P450 isoenzymes may lead to a build-up of clomipramine that could be dangerous.

A variety of augmentation strategies have been proposed, but they are based on the results of small studies and the evidence supporting them is limited. Low doses of conventional antipsychotics (of the order of 0.5–3 mg haloperidol), added to the serotonin reuptake inhibitor, may be helpful in OCD patients with comorbid tics and schizotypal disorders, but not in patients with uncomplicated OCD (Jenike & Rauch, 1994). Antipsychotics such as haloperidol and sulpiride are also used to treat Gilles de la Tourettes' syndrome, and this finding supports the theoretical link between the two disorders. This combination increases the burden of side-effects, including extrapyramidal effects, which may be exaggerated by drug interactions via the aforementioned CYP450 systems. It is wise, therefore, to start treatment with very low doses and increase cautiously according to tolerability.

Newer, atypical neuroleptics have been less successful. Whereas some studies showed that adjunctive risperidone improved responses to SSRIs in resistant patients without tics, there have also been reports that this combination made patients worse. Clozapine has been associated with a worsening of obsessive-compulsive symptomatology. Early promising reports of the effect of augmenting serotonin reuptake inhibitors with buspirone have not stood up to scrutiny under controlled conditions. Nor is there evidence that augmentation with lithium has a role in OCD. Electroconvulsive therapy is generally unhelpful.

Although most benzodiazepines are ineffective, clonazepam was seen to be as effective as clomipramine in a small, controlled crossover study, suggesting a possible role for this drug as an augmentation agent. Small studies have also suggested a possible role for L-tryptophan, the amino acid precursor of serotonin. Unfortunately, investigation of L-tryptophan was suspended owing to its association with the toxic eosinophilia-myalgia syndrome, and the drug is now only available on a named patient basis. Further exploration of L-tryptophan would be welcome.

Inositol (18 g/day) is an experimental compound that has shown some evidence of mild anti-obsessional efficacy. Its pharmacological actions are not well-understood, but it is thought to be involved in intracellular messenger systems. Preliminary reports hint at a possible role for inositol as an augmentation agent.

There are conflicting data on the value of adding the serotonergic beta-blocker pindolol. Antiepileptic drugs such as sodium valproate and gabapentin are currently being investigated in OCD. These

compounds are theoretically interesting, since some experts believe OCD involves a failure of intracortical neuronal inhibition that may be reversed by these drugs. Optimistic reports of the effects of the anti-androgenic drug cyproterone acetate need to be subjected to further controlled investigation.

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## Exposure therapy and OCD

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Exposure therapy has been established as an effective treatment for OCD in a small number of controlled studies of variable methodological rectitude (Lindsay *et al*, 1997). Treatment requires roughly 20 hours of specialist time, and because few centres offer it, there are long waiting-lists. Group exposure merits further investigation. The lack of positive controlled trials looking at cognitive therapy suggests that, despite its popularity, there is no advantage for this treatment in OCD (James & Blackburn, 1995).

The available evidence suggests that exposure therapy is associated with similar rates of treatment response as drug treatment, although properly controlled studies comparing the two treatments head-to-head have not been performed (reviewed in Fineberg & Drummond, 1995). Exposure is less likely to be effective in patients with very severe illness, predominant obsessions or significant levels of comorbid depression, and pharmacotherapy is considered the treatment of choice for these patients. Patients who have failed to respond to exposure have been shown to respond well to pharmacotherapy.

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## Combining pharmacotherapy and behaviour therapy

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Obsessive-compulsive patients are particularly concerned about the long- and short-term side-effects of treatment. At the outset, many are unwilling to tolerate the anxiety associated with exposure, but, once drug treatment is underway, they are usually more willing to face their fears. Similarly, up to 10% of patients initially refuse pharmacotherapy, but, once engaged in exposure therapy, many accept medication. The basic principles of exposure are relatively easy to impart in the general psychiatric clinic, and an integrated approach is advocated by most authorities for most patients.

It is, therefore, surprising that the effects of combining drug treatment with exposure has received so little systematic investigation. Although it appears clear that the two forms of treatment do

not interfere with each other, we do not know to what extent the combination adds to the effect of monotherapy. Three small studies demonstrated that administration of a serotonin reuptake inhibitor led to greater improvement in patients receiving exposure therapy (Marks *et al*, 1980; Cottraux *et al*, 1990; Hohagen *et al*, 1998). In the study by Cottraux *et al* (1990), the combination was no better than fluvoxamine given alone, but the other studies were not designed in a way that allowed a comparison between drug monotherapy and combination treatment. Thus, we know that combined SSRI and exposure can be more effective than exposure alone. However, we do not know whether it is more effective than SSRI alone, although in practice, there are many patients who improve further when exposure is added.

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## Multiple choice questions

1. Obsessive-compulsive disorder:
- affects women more than men in a ratio 1.5:1
  - affects 3% of the population in their lifetime
  - affects 0.1% of the population in their lifetime

- usually runs an episodic course punctuated by remissions
- is associated with an increased risk of suicide.

2. SSRIs in OCD:

- are more effective in higher doses
- are not helpful for treating compulsions
- are recommended for treating children
- are not as effective as clomipramine in severe cases
- are associated with a transient increase in symptoms in the first days of treatment.

3. Depression in OCD:

- affects two-thirds of cases at some point
- responds better to a serotonin reuptake inhibitor than to any other form of antidepressant
- predicts a poor response to pharmacotherapy
- if severe, predicts a poor response to exposure
- should be treated with lithium.

4. Exposure treatment in OCD:

- is more effective for compulsions than obsessions
- is less effective in depressed patients
- is positively augmented by serotonin reuptake inhibitor drugs
- is contraindicated in patients receiving drug treatment
- when it fails predicts a poor response to serotonin reuptake inhibitor drugs.

5. Long-term drug treatment in OCD:

- is recommended for most cases
- protects against relapse as long as it continues
- is associated with sexual dysfunction in 30% cases
- is poorly tolerated by most patients
- requires the same high dose levels as acute treatment.

### MCQ answers

1	2	3	4	5
a T	a T	a T	a T	a T
b T	b F	b T	b T	b T
c F	c T	c F	c T	c T
d F	d F	d T	d F	d F
e T	e F	e F	e F	e T