Advanced Interventions Service
Ninewells Hospital & Medical School | Dundee | Scotland, UK
www.advancedinterventions.org.uk

"It looks easy, but it's anything but…"

Treatment guidelines for the management of Obsessive-Compulsive Disorder (OCD) in secondary care

Dr David Christmas, Consultant Psychiatrist

Professor Keith Matthews, Professor of Psychiatry and Honorary Consultant Psychiatrist

Contents

1. Introduction

1.1 Foreword

These guidelines are not intended to replace existing evidence-based guidelines for the management of OCD. Indeed, many of the treatment recommendations mirror existing guidelines and for the early stages of treatment the national guideline groups have done substantial literature reviews and meta-analyses to determine comparative effectiveness of treatments. Consequently, the early treatment recommendations are entirely consistent with existing guidelines.

However, we recognise that current guidelines often fail to provide robust guidance beyond the first few treatment steps and they usually attempt to cover all severities of illness, and across all healthcare settings. This is probably more helpful for healthcare commissioners than it is for psychiatrists in secondary care (where most of their patients have already exhausted most of the treatment steps).

Further, it is recognised that unless guidelines are updated very regularly, they can become out-of-date. Importantly, new studies which may influence clinical decision-making do not get incorporated until the guidelines are reviewed. This document is an attempt to provide a set of treatment recommendations to practising clinicians that can be updated when new evidence emerges.

1.2 Who are these guidelines intended for?

These guidelines are intended for psychiatrists in secondary-care mental health services. Therefore, it is anticipated that most patients will have tried (and failed to respond to) a number of first- and possibly second-line treatments for OCD by the time that they reach community mental health teams (CMHTs).

Rather than providing a detailed meta-analysis of controlled trials, these guidelines are intended to be relevant to the practising clinician. Key information is summarised in tables, and relevant 'good practice points' and treatment recommendations are highlighted.

1.3 Structure of these guidelines

These guidelines have several sections:

1. Some general principles of treating OCD;
2. Specific treatment steps. Alongside recommendations for treatment, common issues are discussed in a 'Frequently-Asked Questions' format;

3. Some discussion about 'novel' treatments so that the clinician has some information to judge the likely benefits (and risks) of 'small-print' treatments;
4. A section on troubleshooting common issues;
5. Some appendices with further information on whom to approach for further information and advice and more intensive treatment options for patients.

1.4 Further reading

Current guidelines for the treatment of OCD should be consulted at all stages of treatment. Existing guidelines include those from: National Institute of Health and Care Excellence (2006); the Anxiety Disorders Association of Canada (2014) and the American Psychiatric Association (2007). Additional narrative reviews of treatments are also available (Fineberg & Gale, 2005; Fineberg, Reghunandanan, Brown, *et al*, 2013).

2. General Principles of Management

A1. Rating scales are your friend

Rating scales are extremely useful in determining levels of severity and assessing the response to treatment. Most studies don't include patients with very severe or extreme symptoms, and you should be prepared to make judgements about the generalisability of study findings to your patient(s).

The 'gold standard' rating scale for OCD is the Yale-Brown Obsessive-Compulsive Scale (YBOCS; Goodman, Price, Rasmussen, *et al*, 1989a; Goodman, Price, Rasmussen, *et al*, 1989b). It comes in clinician-rated and self-report versions, with the latter demonstrating satisfactory validity against the clinician-rated version (Steketee, Frost & Bogart, 1996). Other rating scales that may be helpful in OCD include: PADUA-Revised (Burns, Keortge, Formea, *et al*, 1996). It is worth noting that different scales measure different dimensions of symptoms and often more than one measure is required (Anholt, van Oppen, Emmelkamp, *et al*, 2009).

We would recommend that rating scales are completed at the beginning of a treatment trial, halfway through, and at the end. This will provide the psychiatrist and the patient with sufficient information to make judgements about the risks and benefits of treatment. A mixture of scales (rating O-C symptoms, quality of life, and other domains such as anxiety and depression) can significantly help decision-making. Some recommendations are given below in **Table 1**.

Table 1 | Recommended rating scales for OCD

Symptom domain	Suggested scales	Sources
Obsessions and Compulsions	Y-BOCS	http://www.stlocd.org/handouts/YBOC-Symptom-Checklist.pdf
	PADUA Inventory (Revised)	http://www.psychologie.tu-dresden.de/i2/klinische/mitarbeiter/materialien/pd-wsur.pdf
Body Dysmorphic Symptoms	Y-BOCS (modified for BDD)	http://www.veale.co.uk/wp-content/uploads/2010/11/BDD-YBOCS-Adult.pdf
Delusional Symptoms in OCD	Brown Assessment of Beliefs Scale (BABS)	http://www.veale.co.uk/wp-content/uploads/2010/11/BABS_revised_501.pdf
Depressive symptoms	Inventory of Depressive Symptoms (IDS)	http://www.ids-qids.org/
	Beck Depression Inventory (BDI) *	http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8018-370
Anxiety symptoms	GAD-7	http://sfaetc.ucsf.edu/docs/gad-7-print.pdf
Global Functioning	Global Assessment of Functioning (GAF)	
Quality of Life	WHO Disability Assessment Scale v2.0	http://www.who.int/classifications/icf/whodasii/en/

* Indicates that scale is licensed and may incur costs.

Further, the use of rating scales can provide valuable evidence about the non-response to a particular treatment. Without reliable data, it can be difficult to retrospectively determine if there was any response to a course of treatment.

2.1 Don't overlook comorbidity

Comorbidity in OCD is extremely common. In some studies, only 7% of patients had OCD exclusively whilst more than one-in-five patients had OCD plus three other conditions (Welkowitz, Struening, Pittman, *et al*, 2000). About 40% of patients have comorbid depression (Torres, Prince, Bebbington, *et al*, 2006; Tükel, Polat, Özdemir, *et al*, 2002). Overall, at least two-thirds of patients will have a comorbid condition.

It is highly-likely that comorbidity results in a less-favourable outcome. The result is that treatable comorbid conditions need to be addressed, and decisions about treatment priorities are often necessary.

A suitable example is someone with comorbid agoraphobia and panic disorder. Whilst their obsessions and compulsions may have responded to ERP, they remain disabled by their symptoms. By treating their agoraphobia with behavioural treatment (graded exposure), they are more able to engage in social activities that can reduce the time spent engaging in rituals.

2.2 Be in it for the long game

OCD, for many people, is a lifelong condition. Relapse is frequent, and symptom persistence is common (Micali, Heyman, Perez, *et al*, 2010; Ross, Fallon, Petkova, *et al*, 2008; Skoog & Skoog, 1999).

The presence of comorbidity complicates treatment, and the duration of each treatment trial necessitates long-term treatment planning. In order to ensure that the patient (and the psychiatrist) can retain hope, clear structured plans for treatment need to be arranged in advance. The psychiatrist needs to be able to describe what treatment steps are available if the current trial is ineffective. If you don't know what to do if the current trial is ineffective, you should be approaching someone who does sooner rather than later!

2.3 It's not drugs *or* ERP – it's both

Unfortunately, availability of high-quality ERP is often limited, and patients (and their families) frequently struggle to access the kind of treatment that patients need. Consequently, it is often quite late before someone receives ERP.

In mild-moderate OCD, of relatively short duration (< 1-2 years), response to ERP (delivered in a group, using supported teletherapy, or directly supervised by a therapist) may be effective. However, where someone is profoundly disabled by their symptoms, and where they have had OCD for many years (or even decades), behavioural treatment alone may be insufficient to achieve clinically-significant improvements.

Surprisingly, there are relatively few high-quality studies that have compared psychological and pharmacological treatments alone and in combination. When NICE reviewed the literature, they concluded that: *"The evidence from five studies suggests that there is greater improvement for OCD symptoms from combined SRIs and ERP when compared with ERP alone. There is also evidence from a single study that the combination may be better than SRI alone (clomipramine in this case). These results suggest that adults with OCD should be offered the possibility of combined treatment. However, the evidence to date is from simultaneous combined treatment and we do not know whether*

this is the best way of using the two treatments together." (National Institute for Health and Clinical Excellence, 2006).

Our clinical recommendation is that patients with moderate-to-severe symptoms (Y-BOCS scores typically above 26), and/or marked functional impairment, and who are not making satisfactory progress with either pharmacological or behavioural treatment alone should have access to combined treatment (drugs + behavioural treatment, ERP).

2.4 Severity of OCD is likely to affect treatment choice

It is more than likely that treatments with evidence of efficacy/effectiveness in milder forms of OCD are less effective in more severe forms of the illness. For example, many treatments that show benefit in mild to moderate depression (*e.g.* CBT) have much less effect in severe depression. Similarly, Clozapine is no better than Chlorpromazine in treatment-naïve schizophrenia, but in treatment-refractory schizophrenia, it has greater benefit.

The importance of this observation is that treatment decisions need to be informed by an understanding of the severity and chronicity of symptoms. A recent study comparing the addition of ERP or Risperidone to and SSRI found that ERP had greater efficacy (Simpson, Foa, Liebowitz, *et al*, 2013). The evidence for ERP in OCD is robust and it should not be the case that patients should have to choose between behavioural and drug treatment.

However, it is not known if these findings can be generalised to all patients with OCD. In the Simpson study, only 7% of patients had previous exposure to any kind of ERP – the patients were ERP-naïve and this figure is likely to be higher in most NHS settings. Further, the baseline Y-BOCS score was 26 – those with more severe symptoms and with previous exposure to ERP may not show a preferential response for [further] ERP.

2.5 Therapists need to be trained in the treatments they are providing

The current NICE guidelines (2006) state that: "*All healthcare professionals offering psychological treatments to people of all ages with OCD or BDD should receive appropriate training in the interventions they are offering and receive ongoing clinical supervision in line with the recommendations in Organising and Delivering Psychological Therapies*[1]*...*"

[1] http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4086100

ERP is not an easy intervention to deliver, particularly because it involves deliberately exposing the patient to anxiety-provoking situations. The prevailing ethos of most services and the natural instincts of most therapists is to reduce anxiety, rather than increase it (albeit temporarily). This creates a range of conflicts for the therapist. The identification of skilled local therapists who are able to deliver ERP is an important part of any service treating OCD.

2.6 Is CBT as good as ERP? Aren't they the same thing?

In a word: "*no*". In the US literature, ERP is often referred to as CBT or CBT/ERP whereas in the UK, CBT is something different. However, in the US studies, the descriptions of the interventions indicate that the treatment is very much behavioural – it is much closer to classic ERP than cognitive-behavioural approaches tend to be in the UK.

Whilst CBT (in the American style) is effective, it is the 'B' part of the CBT (rather than the 'C' part) that is likely to be most effective. Many therapists continue to argue that cognitive approaches to OCD can be just as effective as behavioural treatment, but some of the treatment efficacy may rely on the expertise of the cognitive therapist and many of the approaches (such as behavioural tests) in CBT are inherently behavioural in nature.

A number of trials have compared Cognitive Therapy (CT) to behavioural therapy (ERP) (Cottraux, Note, Yao*, et al*, 2001; McLean, Whittal, Thordarson*, et al*, 2001; van Oppen, de Haan, van Balkom*, et al*, 1995). In most, CT was generally as effective as ERP, but there was evidence of greater treatment efficacy for ERP with longer follow-up.

However, it is likely that CT can enhance the effectiveness of behavioural approaches, and behavioural experiments increase the effectiveness of more cognitive-based therapy (Abramowitz, 2006).

2.7 Target doses for drug treatment

The following are recommendations only and are based on the APA Guidelines (American Psychiatric Association, 2007). A balance needs to be found between the maximum (or maximum-tolerated) dose and adverse effects. This can only be determined by careful exploration and experimentation, and it has to be a collaborative process.

The rationale for higher doses should be discussed with the patient, and where doses exceed licensed doses, you should document that appropriate discussions have taken place. Close monitoring of tolerability should occur.

Table 2 | Target doses of antidepressants used to treat OCD

Drug	Usual Target Dose (mg/day)	Usual Maximum Dose (mg/day)
Citalopram [1]	40-60	80
Clomipramine [2]	150-250	250
Escitalopram [1]	20-30	40
Fluoxetine	60	80-100
Fluvoxamine	200	300
Paroxetine	40-60	60
Sertraline	200	250-300

[1] Please note that recent 'black box' warnings will necessitate caution with higher doses of Citalopram/Escitalopram, particularly in those with cardiac problems or a previous history of QT_c prolongation. ECG monitoring should be considered for the majority of patients on high doses.

[2] Clomipramine can be poorly tolerated, particularly if the starting dose is too high and/or the rate of dose increase is too great. This may result in a 'failed' trial of Clomipramine.

2.8 Choosing drugs

A number of factors should inform treatment choices. Although not exhaustive, these are summarised below in **Table 3**.

Table 3 | Comparison of SRIs used to treat OCD

Drug	Advantages	Disadvantages
Citalopram	1. Usually fairly-well tolerated 2. Doesn't inhibit the metabolism of other drugs	1. Requires ECG monitoring at higher doses
Clomipramine	1. Probably the most effective drug for OCD	1. Can be poorly-tolerated if dose or rate of increase is too high 2. Dose titration period can be longer than other drugs and requires closer supervision
Escitalopram	1. Usually fairly-well tolerated 2. Doesn't inhibit the metabolism of other drugs	1. Requires ECG monitoring at higher doses 2. Although it is the active ingredient of Citalopram, it has less evidence for treating OCD than other SSRIs
Fluoxetine	1. Usually fairly-well tolerated, particularly at higher doses 2. Good evidence of efficacy 3. Recommended by NICE where BDD symptoms are prominent	1. Can inhibit the metabolism of other drugs, causing interactions 2. Long half-life requires caution when switching

Drug	Advantages	Disadvantages
Fluvoxamine	1. Well reported in the literature	1. Probably not the best-tolerated SSRI 2. Not commonly-used these days
Paroxetine	1. Robust evidence of benefit for treatment of OCD	1. Can inhibit the metabolism of other drugs, causing interactions 2. Short half-life can lead to increased anxiety and discontinuation if doses are missed
Sertraline	1. Usually fairly-well tolerated 2. Doesn't inhibit the metabolism of other drugs	

3. Treatment Steps

3.1 Step 1: SSRIs

3.1.1 Evidence base to support Step 1

SSRIs are the first-line pharmacotherapy for OCD and are first line treatment in major guidelines. NICE recommend that: "*For adults with OCD, the initial pharmacological treatment should be one of the following SSRIs: fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram*[2]." (National Institute for Health and Clinical Excellence, 2006).

Overall, SSRIs offer the best balance between efficacy and tolerability and should be considered first-line for the treatment of OCD.

3.1.2 Are all SSRIs equal?

With regards to differences between SSRIs, there is little very convincing evidence that some SSRIs are more efficacious, although some have slightly more evidence to support their use. The drugs currently recommended as first line treatment by NICE (2006) are: fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram.

3.1.3 When should you increase the dose?

The NICE recommendation is to increase the dose after 4-6 weeks if there has been no evidence of response, and the drug is well tolerated. In patients with a history of treatment resistance, it may be appropriate to start increasing the dose (depending on tolerability) earlier on, with an expectation that early response is unlikely and there is a

[2] Citalopram does not have marketing authorisation for treatment of OCD. In addition, there are additional cardiac risks that require monitoring.

desire to move as quickly as possible through treatment steps. Such a decision should be a collaborative one which is made after consideration of the risks and benefits.

3.1.4 Are high doses necessary?

Essentially, yes. In contrast to the treatment of depression, SSRIs show a definite dose-response relationship in the treatment of OCD (Bloch, McGuire, Landeros-Weisenberger, *et al*, 2010; Ninan, Koran, Kiev, *et al*, 2006; Pampaloni, Sivakumaran, Hawley, *et al*, 2010).

It is also clear that adverse effects are greater with higher doses, and the aim of the clinician should be to help the patient achieve the maximum tolerable dose for an adequate duration of time.

3.1.5 Is it worth switching to a different SSRI?

There is some evidence that switching from an SSRI to a SNRI may be associated with greater response (Dell'Osso, Mundo, Marazziti, *et al*, 2008; Denys, van Megen, van der Wee, *et al*, 2004). In one of these studies, switching from Venlafaxine to Paroxetine increased response rates.

However, the evidence is inconclusive (and to some extent, contradictory regarding SSRI > SNRI or SNRI > SSRI). Where there is poor tolerability to one SSRI (e.g. Paroxetine), switching to another SSRI (e.g. Sertraline) may increase the likelihood that the patient can tolerate an adequate trial. Where the patient has completed an adequate trial (in dose and duration), there is probably little evidence to support switching to a different SSRI; particularly since each trial of medication in OCD may take up to 4-5 months (including dose escalation and withdrawal). In most cases, it is likely to be advantageous to switch to the next step options.

3.2 Step 2: Clomipramine

3.2.1 Is Clomipramine more effective than other SRIs?

The APA Guidelines acknowledge that meta-analyses of placebo-controlled RCTs appear to demonstrate that Clomipramine is more efficacious than fluoxetine, fluvoxamine, and sertraline. However, head-to-head trials of drugs do not support this conclusion.

It may be the case that in more chronic forms of the illness, or with greater severity, Clomipramine may be more effective (*c.f.* Clozapine in Schizophrenia) but there is little evidence to confirm this.

3.2.2 Many patients don't seem to tolerate it. What can I do to increase tolerability?

The basic principles are start low, and go slow. A starting dose of 50mg per day, increasing every 3-5 days to 200mg/day is likely to be poorly-tolerated by most people. The APA suggest that the starting dose (and incremental dose) of Clomipramine is 25mg/day. However, we would suggest that dose increases of Clomipramine should probably be no greater than 25mg every 5-7 days. The exception would be someone who is experiencing no adverse effects.

3.3 Step 3a: Augmentation with antipsychotics

3.3.1 Which is the best antipsychotic to augment with?

The answer to this question isn't clear, since conclusions from meta-analyses are contradictory with regards to some antipsychotics. The findings from meta-analyses are summarised in Table 4.

Table 4 | Strength of Evidence for antipsychotic augmentation of SRIs

Study	Risperidone	Quetiapine	Aripiprazole	Olanzapine	Haloperidol
Bloch (2006)	+	?	N/A	?	+
Skapinakis (2007)	+	-	N/A	-	?
Komossa (2010)	+	? [1]	N/A	-	N/A
Dold (2013)	+	-	?	-	?

+ Evidence of benefit

? Uncertain Evidence of benefit

- Evidence of lack of efficacy

[1] No effect on primary outcome (response rate) but some evidence of effect on anxiety and depressive symptoms.

Definite conclusions are difficult to make. Risperidone has the greatest evidence of efficacy and should be considered the first-line augmentation strategy. There is at least one RCT of Aripiprazole augmentation (Sayyah, Sayyah, Boostani, *et al*, 2012) but evidence from meta-analyses isn't available. Quetiapine has not demonstrated clear efficacy in meta-analyses, but a Cochrane Review (2010) found some evidence of improvement in anxiety and depressive symptoms. There are a number of controlled

trials supporting the use of Quetiapine (Denys, de Geus, van Megen, *et al*, 2004; Diniz, Shavitt, Pereira, *et al*, 2010); however, not all trials are positive (Carey, Vythilingum, Seedat, *et al*, 2005; Diniz, Shavitt, Fossaluza, *et al*, 2011). Olanzapine has insufficient evidence to recommend it as an augmentation strategy for OCD. Haloperidol is only supported by a small number of trials, and whilst it has evidence of efficacy, it is often less tolerable than Risperidone. It may be considered when there are comorbid tics present.

Pragmatic clinical recommendations are as follows:

1. First line: Risperidone;
2. Second line: Aripiprazole or Quetiapine. The choice should be made based on adverse effects and tolerability;
3. There is insufficient evidence to recommend Olanzapine as a treatment for OCD at the current time.

3.3.2 What sorts of doses are appropriate?

In general, the doses used to augment SRIs for the treatment of OCD are lower than those used to treat schizophrenia and other psychotic disorders. There is little evidence to support higher doses unless the patient is tolerating the medication and is showing evidence of greater response at higher doses. Typical target doses are:

Risperidone: 1-3mg/day
Aripiprazole: 5-10mg/day
Quetiapine: 150-300mg/day

3.3.3 Are all antipsychotics worth trying?

No. Please see discussion above.

3.3.4 Can I augment any SRI with antipsychotics?

Although most trials involve the augmentation of SSRIs, in practice it is common to augment any antidepressant used to treat OCD with antipsychotic drugs.

3.3.5 Should I stop the antipsychotic before changing the SRI?

Whilst it is tempting to do so, there is probably little robust evidence (and not much clinical experience) to support the expectation that someone who has failed to respond to a robust trail of an SRI + antipsychotic will show a convincing response to a different SRI alone. Whilst the final decision belongs to the patient, the expectations of the

clinician should be explained so that the patient can make a fully-informed choice. In some situations, where the patient has poorly-tolerated the antipsychotic, there is a stronger argument for stopping the antipsychotic at the same time as switching.

However, where the antipsychotic is reasonably well-tolerated, and where several trials of monotherapy have been unsuccessful, there is a stronger argument for continuing the antipsychotic whilst switching SRIs. This has several benefits: first, there may be some modest reduction in symptoms that makes switching easier; second, it can shorten the overall time required to determine benefit from any trial.

For example, compare the two situations below:

	Monotherapy then augmentation	**Continue antipsychotic whilst switching**
Time to reduce SRI	4 weeks	4 weeks
Time to switch and titrate dose of SRI upwards	6 weeks	6 weeks
Time at maximum dose	12 weeks	12 weeks
Time to titrate dose of antipsychotic (assuming non-response)	4 weeks	-
Time at maximum dose	8 weeks	-
Total time to achieve further trial of SRI + antipsychotic augmentation	34 weeks	22 weeks

It can be seen that the total time on the SRI counts towards the total time of augmentation in the second case.

The main disadvantage of this approach is that the risk of adverse effects is increased. The advantages and disadvantages of both approaches should be discussed with the patient, bearing in mind that the likelihood of response to monotherapy after 2-3 failed treatment trials is poor.

3.4 Step 3b: Augmentation with other drugs

3.4.1 Introduction

Many patients may be unwilling to consider antipsychotic drugs due to concerns over adverse effects, or a lack of understanding about why these drugs might be helpful in OCD. There are some other drugs that have an emerging evidence base in the treatment

of OCD. NICE, in their evidence update, concluded that: "*The anticonvulsant drugs lamotrigine and topiramate may result in improved OCD symptoms as add-on therapy to SSRIs compared with SSRIs plus placebo, but further research is needed. Topiramate may be associated with increased adverse events.*" (National Institute for Health and Care Excellence, 2013).

3.4.2 Lamotrigine

A recent RCT of Lamotrigine augmentation reported benefits for Lamotrigine augmentation of SRIs compared to placebo; with additional positive effects on mood symptoms (Bruno, Micò, Pandolfo*, et al*, 2012).

3.4.3 Topiramate

There are at least two RCTs of Topiramate augmentation of SRIs (Berlin, Koran, Jenike*, et al*, 2011; Mowla, Khajeian, Sahraian*, et al*, 2010). Whilst benefits are reported, the drug tends to be poorly tolerated and it cannot be recommended for mainstream treatment of OCD.

3.4.4 D-Cycloserine

There are a small number of studies reporting additional beneficial effects when behavioural treatment is augmented with D-Cycloserine (Kushner, Kim, Donahue*, et al*, 2007; Storch, Murphy, Goodman*, et al*, 2010). However, it remains unclear whether this treatment has any place in mainstream treatment and it has only been used in addition with behavioural therapy. It should not be considered an effective augmentation agent alongside other medications.

3.5 Steps 4-6: Systematic trials of SRI ± augmentation

3.5.1 Introduction

After the first few treatment steps, there is little evidence to make definitive treatment recommendations. Treatment entails systematic trials of further SRIs, either in combination or augmented by antipsychotics, combined with ERP, and with prospective monitoring of symptoms.

3.5.2 Clomipramine + SSRI

A number of case series report additional benefits of combination therapy in a range of ages (Browne, Horn & Jones, 1993; Figueroa, Rosenberg, Birmaher*, et al*, 1998; Simeon, Thatte & Wiggins, 1990).

There are a number of open-label and blinded randomised trials of Clomipramine in combination with an SSRI.[3] In one trial, fluoxetine + clomipramine was superior to fluoxetine + placebo or fluoxetine + quetiapine (Diniz, Shavitt, Fossaluza, *et al*, 2011), but the interaction between fluoxetine and the metabolism of clomipramine meant that increased levels of clomipramine could have been responsible for the additional benefit. In an open (but randomised) trial of clomipramine + citalopram, the combination was found to be superior to either drug alone (Pallanti, Quercioli, Paiva, *et al*, 1999). Not all studies are positive, however. In an earlier study of SSRI + clomipramine versus SSRI + quetiapine, the additional of clomipramine didn't result in further reductions in symptom scores, whereas the addition of quetiapine did (Diniz, Shavitt, Pereira, *et al*, 2010).

3.5.3 Venlafaxine

There is some evidence from open-label studies that venlafaxine may be as effective for OCD as clomipramine and may be beneficial if patients have failed to respond to a trial of an SSRI (Albert, Aguglia, Maina, *et al*, 2002; Hollander, Friedberg, Wasserman, *et al*, 2003). However, a double-blind switch study comparing Paroxetine to Venlafaxine found that, "…*paroxetine was more efficacious than venlafaxine in the treatment of nonresponders to a previous SRI trial*" (Denys, van Megen, van der Wee, *et al*, 2004).

We suggest that Venlafaxine can be considered where patients have not responded to other SRIs, but the evidence base is somewhat contradictory and switching to other SRIs may be just as effective. Where a patient has not had an adequate trial of antipsychotic augmentation, this should probably be tried first because of the greater evidence base.

3.6 Novel treatments

3.6.1 Introduction

Novel treatments should only be considered under the following circumstances:

1. The patient has failed to respond to all other trials of SRIs, augmentation, and robust trials of ERP;
2. The team has experience in the management of severe and/or chronic OCD;
3. The prescriber has experience in using the agents listed;
4. Informed consent has been obtained, and the risks/benefits of 'off-label' prescribing have been discussed with the patient;

[3] Usually Citalopram because it doesn't inhibit the metabolism of Clomipramine.

5. Such trials are part of a carefully-structured treatment plan that addresses the medium- and long-term strategies that will be considered. They should not be substituted for a lack of availability of other, more established, treatments.

3.6.2 Memantine

There is only open-label and case study data reporting outcomes from trials of memantine in OCD (Aboujaoude, Barry & Gamel, 2009; Feusner, Kerwin, Saxena, *et al*, 2009; Poyurovsky, Weizman, Weizman, *et al*, 2005; Stewart, Jenike, Hezel, *et al*, 2010).

It is not possible to recommend memantine at the current time due to lack of evidence from more robust clinical trials.

3.6.3 Riluzole

Riluzole is a glutamatergic drug. Alongside a case-report relating to augmentation with riluzole (Mahgoub, Asemota & Alexopoulos, 2011), there is an RCT comparing treatment with fluvoxamine + riluzole versus fluvoxamine + placebo (N=50). Those receiving riluzole had a slightly greater reduction in YBOCS score at 10 weeks (mean difference 3.56; effect size = 0.59). The authors concluded that, "*Riluzole may be of clinical use as an adjuvant agent to fluvoxamine in treatment of moderate to severe obsessive–compulsive disorder.*" (Emamzadehfard, Kamaloo, Paydary, *et al*, 2016)

However, the use of riluzole for the treatment of OCD is off-label and experience in the use of this drug is essential.

3.6.4 Ondansetron

There is one small open study (Pallanti, Bernardi, Antonini, *et al*, 2009) and one RCT (Soltani, Sayyah, Feizy, *et al*, 2010) of ondansetron augmentation in OCD. Studies have reported positive outcomes and good tolerability and whilst ondansetron appears to be well-tolerated, insufficient information is available to make a definitive recommendation.

3.6.5 Nicotine

Nicotine (in the form of transdermal patches) has been used as an augmentation strategy for Tourette syndrome for many years and there is outcome data from open studies to support its use in this disorder (Howson, Batth, Ilivitsky, *et al*, 2004). However, little is known about benefits for OCD and recommendations cannot be made.

3.6.6 N-Acetylcysteine

There is one RCT comparing N-Acetylcysteine augmentation to placebo augmentation of SRIs (Afshar, Roohafza, Mohammad-Beigi, *et al*, 2012). Compared to placebo, the drug

demonstrated superiority on the Y-BOCS score and CGI-S score, but not the CGI-I score. There is insufficient information with which to make a clear recommendation and the drug doesn't have a license for this indication in the UK.

3.6.7 Minocycline

There is one RCT comparing minocycline augmentation of fluvoxamine with placebo (N=102). Patients had severe OCD (mean baseline YBOCS = 29.93 ± 4.03) and at 10 weeks there was a mean difference between groups of 3.21points on the YBOCS, with an effect size of 0.56 (Esalatmanesh, Abrishami, Zeinoddini, *et al*, 2016).

Whilst treatment was fairly well tolerated, the use of minocycline as a treatment option should be avoided until there is more accumulated evidence.

3.7 Summary of novel treatments

A summary of the above discussions is shown in the table below. With the exception of nicotine (which can be bought over-the-counter as a smoking cessation aid), none of these medications are licensed for use in OCD.

Table 5 | Level of recommendation for various augmentation strategies

Augmentation agent	Level of evidence	Effective in the studies reported?	Licensed for OCD?	Is there sufficient evidence that benefits > risks?
Memantine	Open label study	Yes	No	No
Riluzole	RCT	Yes	No	No
Ondansetron	RCT	Yes	No	Possibly
Nicotine	Case series	Yes	N/A (not a prescription-only medication)	Possibly
N-Acetylcystine	RCT	On some measures	No	No
Minocycline	RCT	Yes	No	Possibly

4. Specific types of OCD

4.1 Drug treatment of hoarding

Many would argue that hoarding does not respond favourably to pharmacological treatment. However, recent reviews have argued that many cases do show some

improvement with SRIs and that the preferred treatment strategy should be a combination of medication and behavioural therapy (Saxena, 2011).

4.2 Body-Dysmorphic Disorder (BDD)

4.2.1 Psychological therapy

The mainstay for treating BDD is CBT/ERP. Recent meta-analyses confirm that CBT has clinical benefits, although longer-term effects are unknown (Harrison, de la Cruz, Enander, *et al*, 2016). Treatment delivered by an experience therapist is important due to the high rates of comorbidity with other mood and anxiety disorders and also personality disorders (Veale, Boocock, Gournay, *et al*, 1996).

4.2.2 Drug treatment

There is evidence to support the use of drug treatment in the treatment of BDD (Phillips & Hollander, 2008; Veale, 2004). NICE (2006) recommendations are that:

- "*Adults with BDD with moderate functional impairment should be offered the choice of either a course of an SSRI or more intensive individual CBT (including ERP) that addresses key features of BDD.*"
- *"Adults with BDD with severe functional impairment should be offered combined treatment with an SSRI and CBT (including ERP) that addresses key features of BDD.*"

The SSRI with the greatest evidence of effectiveness in BDD is fluoxetine (National Institute for Health and Clinical Excellence, 2006). It should be noted that there is no evidence for antipsychotics in BDD and their use should be avoided.

4.3 Psychotic symptoms in OCD ('Schizo-OCD')

There is an increased risk of comorbidity with schizophrenia in people with OCD (Cederlöf, Lichtenstein, Larsson, *et al*, 2015) and many people with OCD will present with patterns of thinking and/or deficits in insight that appear more characteristic of a psychotic illness than OCD. Indeed, DSM-5 now has a number of specifiers such as: "*With poor insight (The individual thinks obsessive-compulsive disorder beliefs are probably true); With absent insight/ delusional beliefs (The individual is completely convinced that obsessive-compulsive disorder beliefs are true).*" (American Psychiatric Association, 2013)

However, people with OCD generally don't have other psychotic symptoms such as hallucinations or thought disorder and careful assessment is required sometimes to

determine if the individual is presenting with OCD with quasi-psychotic symptoms or has comorbid OCD and schizophrenia.

The key question for the clinician is whether antipsychotic augmentation should be considered earlier in the pathway than usual. In some situations, antipsychotic augmentation may result in both an improvement in O-C symptoms (and/or reductions in anxiety) but also improvements in insight that may make it easier to deliver behavioural treatment.

4.4 Pure obsessions ('Pure-O')

It is probably more helpful to think of 'Pure-O' as simply being the absence of overt compulsive behaviour since almost all people will have some form of compulsion (albeit mental) associated with the thoughts or intrusions. The absence of overt compulsions can often appear as constant worry, resulting in the OCD as being misidentified as generalised anxiety disorder.

Treatment for predominantly obsessional OCD is broadly similar to that of mixed obsessions and compulsions. However, due to the internalised nature of the symptoms there is often more of a cognitive focus than in-vivo exposure. Despite this, successful treatment will almost certainly need to incorporate a range of behavioural experiments as well as exposure to situations that trigger the obsessions.

5. Troubleshooting

5.1 My patient can only tolerate high doses for short periods of time

It is more important to have a trial of maximum-tolerated dose for ≥ 12 weeks than it is to have a short trial of maximum dose. For example, a 16-week trial of 200mg/day of Clomipramine tells you more about treatment response than a two-week trial of 300mg/day of Clomipramine.

In most cases, patients should be advised to reduce (rather than stop) the dose if adverse effects become problematic. In many cases, tolerability to adverse effects develops over time and further dose escalation can be attempted again.

5.2 My patient can't tolerate anything

Some patients do report an inability to tolerate any SRI; let alone with doses known to be therapeutic in OCD. This creates challenges because they are often referred on to specialist centres when they haven't had an adequate trial of any drug and there is uncertainty about whether previous drug trials have been adequately explored.

We would recommend that patients be advised that they need to be prepared to try all SRIs to demonstrate that they are truly unable to tolerate any drug. In many cases, what patients are describing are unpleasant (but often predictable) side effects with serotonergic antidepressants and the most appropriate response to this situation is to commence at a very low dose, and increase very gradually. In such situations, it is probably not appropriate to arrange to review the patient in 3 months – they need very close monitoring and guidance on making changes to doses. In some cases, they may require inpatient admission to ensure a safe environment for dose titration and objective assessment of the severity of adverse effects. For example, was dizziness associated with postural hypotension? Was it some unpleasant GI upset or vomiting and diarrhoea?

Drugs with a wider dose range (*e.g.* Sertraline*)* might be considered and it is worth noting that some SSRIs come in liquid format, and this permits very small dose adjustments to be made. SSRIs that have a liquid preparation in the UK (as of October 2013) are:

- Fluoxetine (generic)
- Seroxat® (Paroxetine)
- Citalopram (generic)
- Cipralex® (Escitalopram)

5.3 Symptoms get so bad when switching that it's impossible to switch

In such situations, there are several options available:

1. *Controlled dose reduction*
    a. It may be more helpful to review the patient more frequently rather than some general advice on reducing the dose. This allows a much closer monitoring of problems, and a greater tailoring of dose reductions.
2. *Short-term use of Benzodiazepines*
    a. Where anxiety levels become too difficult to manage, a short-term prescription of Diazepam can be helpful in reducing anxiety and agitation and may allow the switch of one drug to another
3. *Make sure that you're not causing drug interactions*
    a. Fluoxetine and Paroxetine are both potent inhibitors of Cytochrome P450 2D6. This means that they can increase the concentrations of other drugs metabolised by the same pathway. Consequently, the addition of fluoxetine to Clomipramine may increase clomipramine levels, increase side effects, and give the appearance of poor tolerability of fluoxetine.Appendices

6. Appendices

6.1 Appendix 1: General inclusion criteria for referral to the AIS

1. Diagnosis of Obsessive-Compulsive Disorder made according to ICD-10 (World Health Organisation, 1992), DSM-IV (American Psychiatric Association, 1994), or DSM-5 (American Psychiatric Association, 2013);
    a. Comorbid diagnoses of Obsessive-Compulsive Personality Disorder (OCPD) or Asperger's Syndrome are not absolute contraindications, but they should not be the primary diagnosis and full criteria for OCD should be met. The severity of symptoms should be significant enough to indicate that personality disorder is insufficient to account for the impairments in functioning.
    b. Cases where there is significant diagnostic overlap between OCD and Autism Spectrum Disorder (ASD) may still be seen by the service but it would be expected that there would have been discussion between teams prior to referral.
    c. Similarly, comorbid anxiety disorders (*e.g.* Generalized Anxiety Disorder, Agoraphobia) and depression are common in OCD. These are not a contraindication to referral, but it is expected that efforts have been made to determine that OCD is the primary source of the anxiety symptoms. Such efforts are likely to involve targeted treatment of the other conditions.
2. Symptoms of OCD have persisted for ≥ 2 years without improvement and despite treatment;
3. Severity of OCD, measured using the clinician-rated Y-BOCS, should be ≥ 24 (severe), although in most cases it is likely to be higher;
4. Global Assessment of Functioning (GAF) should be ≤ 50. This means that symptoms are severe and result in *"**serious impairment** in social, occupational or school functioning"*;

6.2 Appendix 2: General exclusion criteria

The service is unable to provide extensive support and/or supervision to patients that do not meet the above inclusion criteria. There is a clear understanding in commissioning arrangements that treatment at steps 1 to 4 in the NICE guidelines will be provided by NHS Boards.

In addition, the provision of 20 hours of exposure and response prevention, delivered in the patient's home, should be available within secondary care MH services as stipulated by the Psychological Therapies Matrix (NHS Education for Scotland, 2015). However, it can be challenging to deliver this in the context of complex and/or chronic OCD and the AIS will aim to facilitate and support local services in delivering this.

6.3 Appendix 3: General treatment criteria

To avoid a single categorical approach to referral, we have described our criteria across a range of interventions and according to a number of domains:

1) *Intervention* – what is the minimum level of treatment within the type of treatment to meet criteria?
2) *Duration* – how long should the patient have received this treatment for to demonstrate non-response?
3) *Confidence* – how confident can we be that the information available is reliable?

6.4 Appendix 4: Detailed treatment criteria for referral

	SRIs	**Augmentation**	**Psychological therapy**	**Family involvement**
Intervention	• Two SRIs given at doses adequate for OCD • Trial of Clomipramine preferred but not essential	• At least one attempted trial of augmentation • Or, augmentation has been discussed with the patient	• At least one attempt at a trial of CBT/ERP (may not have been successful but has clearly been tried)	• Ideally, the family (and/or partner) have had some psychoeducation and have been involved in the treatment
Duration	• At least 8 weeks for each trial	• At least 4-6 weeks	• Minimum of 12 hours' treatment/contact	• More than one session
Confidence	• Reasonable likelihood that information is reliable	• Reasonable likelihood that information is reliable	• Evidence that treatment was delivered in the quantity described • Modality is recognised and consistent with typical models	• Likely that the family have an understanding of OCD and that the treatment plan has involved them to some extent (not required if patient lives alone and/or not close to family)

6.5 Appendix 5: Detailed treatment criteria for entry onto OCD pathway

	SRIs	**Augmentation**	**Psychological therapy**	**Family involvement**
Intervention	• Two SRIs given at doses adequate for OCD • The patient should have had a trial of Clomipramine (or Clomipramine is not tolerated)	• At least one attempted trial of augmentation, one of which should have been Risperidone	• At least one attempt at a trial of CBT/ERP, delivered in the environment where the symptoms are most problematic	• Ideally, the family (and/or partner) have had some psychoeducation and have been involved in the treatment
Duration	• At least 8 weeks for each trial	• At least 4-6 weeks	• At least 16 hours	• More than one session
Confidence	• Reasonable likelihood that information is reliable	• Reasonable likelihood that information is reliable	• High likelihood that the patient hasn't responded to CBT/ERP or evidence that therapy cannot be delivered optimally	• Likely that the family have an understanding of OCD and that the treatment plan has involved them to some extent (not required if patient lives alone and/or not close to family)

6.6 Appendix 5: Detailed treatment criteria for intensive/inpatient treatment

	SRIs	**Augmentation**	**Psychological therapy**	**Family involvement**
Intervention	• At least three SRIs given at doses adequate for OCD • The patient should have had a trial of Clomipramine (or Clomipramine is not tolerated)	• One or more trials of augmentation • At least one trial should have been with Risperidone	• At least one attempt at a trial of CBT/ERP, delivered in the environment where the symptoms are most problematic	• The family have been involved in a range of psychoeducational sessions and there is a good understanding of the systems contributing to the patient's difficulties. • The family and/or partner have been involved in treatment and supporting exposure and response prevention.
Duration	• At least 10-12 weeks for each trial	• At least 6-8 weeks	• In excess of 20 hours	• Approximately 4-6 hours of psychoeducation and/or treatment involvement
Confidence	• Reasonable likelihood that information is reliable	• Reasonable likelihood that information is reliable	• High likelihood that the patient hasn't responded to CBT/ERP	• Sessions have been documented and treatment response is known

6.8 Appendix 5: Detailed treatment criteria for neurosurgical treatment

	SRIs	**Augmentation**	**Psychological therapy**	**Family involvement**
Intervention	• At least three SRIs given at doses adequate for OCD • The patient should have had a trial of Clomipramine (or Clomipramine is not tolerated)	• At least two trials of augmentation • At least one trial should have been with Risperidone • A trial of Clomipramine + antipsychotic should have occurred	• The patient has received a robust trial of intensive and/or prolonged CBT/ERP, including delivery in the environment where the symptoms are most problematic • Sessions are long enough to allow habituation • There is evidence of response prevention having been part of therapy •	• The family have been actively engaged in ERP • This will have involved a systemic understanding of accommodation and numerous trials of the family being involved in supporting the treatment • In most cases, the family involvement will have been a distinct part of treatment
Duration	• At least 10-12 weeks for each trial	• At least 6-8 weeks	• 30-40 hours (or there is robust evidence of non-response at 20 hours of intensive / inpatient therapy)	• 10-12 hours

	SRIs	**Augmentation**	**Psychological therapy**	**Family involvement**
Confidence	• High level of confidence of non-response or intolerability	• High level of confidence of non-response or intolerability	• High likelihood that the patient hasn't responded to CBT/ERP	• Documented evidence of multiple family sessions with records of the extent of enhancement of response and/or barriers to implementation

7. References

Aboujaoude, E., Barry, J. J. & Gamel, N. (2009) Memantine Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder: An Open-Label Trial. *Journal of Clinical Psychopharmacology*, **29**, 51-55. http://dx.doi.org/10.1097/JCP.0b013e318192e9a4

Abramowitz, J. S. (2006) The Psychological Treatment of Obsessive-Compulsive Disorder. *Canadian Journal of Psychiatry*, **51**, 407-416. http://www.ncbi.nlm.nih.gov/pubmed/16838822

Afshar, H., Roohafza, H., Mohammad-Beigi, H., *et al* (2012) N-Acetylcysteine Add-On Treatment in Refractory Obsessive-Compulsive Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of Clinical Psychopharmacology*, **32**, 797-803. http://dx.doi.org/10.1097/JCP.0b013e318272677d

Albert, U., Aguglia, E., Maina, G., *et al* (2002) Venlafaxine versus Clomipramine in the Treatment of Obsessive-Compulsive Disorder: A Preliminary Single-Blind, 12-Week, Controlled Study. *Journal of Clinical Psychiatry*, **63**, 1004-1009. http://www.ncbi.nlm.nih.gov/pubmed/12444814

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)*. Washington, DC: American Psychiatric Press.

---- (2007) Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder. *American Journal of Psychiatry*, **164**, 1-56. http://dx.doi.org/10.1176/appi.books.9780890423363.149114

---- (2013) *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*. Washington, DC: American Psychiatric Press. http://dx.doi.org/10.1176/appi.books.9780890423349

Anholt, G. E., van Oppen, P., Emmelkamp, P. M. G., *et al* (2009) Measuring obsessive-compulsive symptoms: Padua Inventory-Revised vs. Yale-Brown Obsessive Compulsive Scale. *Journal of Anxiety Disorders*, **23**, 830-835. http://dx.doi.org/10.1016/j.janxdis.2009.04.004

Berlin, H. A., Koran, L. M., Jenike, M. A., *et al* (2011) Double-Blind, Placebo-Controlled Trial of Topiramate Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder. *Journal of Clinical Psychiatry*, **72**, 716-721. http://dx.doi.org/10.4088/JCP.09m05266gre

Bloch, M. H., Landeros-Weisenberger, A., Kelmendi, B., *et al* (2006) A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Molecular Psychiatry*, **11**, 622-632. http://dx.doi.org/10.1038/sj.mp.4001823

Bloch, M. H., McGuire, J., Landeros-Weisenberger, A., *et al* (2010) Meta-Analysis of the Dose-Response Relationship of SSRI in Obsessive-Compulsive Disorder. *Molecular Psychiatry*, **15**, 850-855. http://dx.doi.org/10.1038/mp.2009.50

Browne, M., Horn, E. & Jones, T. T. (1993) The benefits of clomipramine-fluoxetine combination in obsessive compulsive disorder. *Canadian Journal of Psychiatry*, **38**, 242-243. http://www.ncbi.nlm.nih.gov/pubmed/8518974

Bruno, A., Micò, U., Pandolfo, G., *et al* (2012) Lamotrigine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-

controlled study. *Journal of Psychopharmacology*, **26**, 1456-1462. http://dx.doi.org/10.1177/0269881111431751

Burns, G. L., Keortge, S. G., Formea, G. M., *et al* (1996) Revision of the Padua Inventory of obsessive compulsive disorder symptoms: Distinctions between worry, obsessions, and compulsions. *Behaviour Research and Therapy*, **34**, 163-173. http://dx.doi.org/10.1016/0005-7967(95)00035-6

Carey, P., Vythilingum, B., Seedat, S., *et al* (2005) Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study [ISRCTN83050762]. *BMC Psychiatry*, **5**, 5. http://www.biomedcentral.com/1471-244X/5/5

Cederlöf, M., Lichtenstein, P., Larsson, H., *et al* (2015) Obsessive-Compulsive Disorder, Psychosis, and Bipolarity: A Longitudinal Cohort and Multigenerational Family Study. *Schizophrenia Bulletin*, **41**, 1076-1083. http://dx.doi.org/10.1093/schbul/sbu169

Cottraux, J., Note, I., Yao, S. N., *et al* (2001) A Randomized Controlled Trial of Cognitive Therapy versus Intensive Behavior Therapy in Obsessive Compulsive Disorder. *Psychotherapy and Psychosomatics*, **70**, 288-297. http://dx.doi.org/10.1159/000056269

Dell'Osso, B., Mundo, E., Marazziti, D., *et al* (2008) Switching from serotonin reuptake inhibitors to duloxetine in patients with resistant obsessive compulsive disorder: a case series. *Journal of Psychopharmacology*, **22**, 210-213. http://dx.doi.org/10.1177/0269881107079865

Denys, D., de Geus, F., van Megen, H. J., *et al* (2004) A Double-Blind, Randomized, Placebo-Controlled Trial of Quetiapine Addition in Patients with Obsessive-Compulsive Disorder Refractory to Serotonin Reuptake Inhibitors. *Journal of Clinical Psychiatry*, **65**, 1040-1048. http://www.ncbi.nlm.nih.gov/pubmed/15323587

Denys, D., van Megen, H. J., van der Wee, N., *et al* (2004) A Double-Blind Switch Study of Paroxetine and Venlafaxine in Obsessive-Compulsive Disorder. *Journal of Clinical Psychiatry*, **65**, 37-43. http://www.ncbi.nlm.nih.gov/pubmed/14744166

Diniz, J., Shavitt, R., Pereira, C., *et al* (2010) Quetiapine versus clomipramine in the augmentation of selective serotonin reuptake inhibitors for the treatment of obsessive-compulsive disorder: a randomized, open-label trial. *Journal of Psychopharmacology*, **24**, 297-307. http://dx.doi.org/10.1177/0269881108099423

Diniz, J. B., Shavitt, R. G., Fossaluza, V., *et al* (2011) A Double-Blind, Randomized, Controlled Trial of Fluoxetine Plus Quetiapine or Clomipramine Versus Fluoxetine Plus Placebo for Obsessive-Compulsive Disorder. *Journal of Clinical Psychopharmacology*, **31**, 763-768. http://dx.doi.org/10.1097/JCP.0b013e3182367aee

Dold, M., Aigner, M., Lanzenberger, R., *et al* (2013) Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *International Journal of Neuropsychopharmacology*, **16**, 557-574. http://dx.doi.org/10.1017/S1461145712000740

Emamzadehfard, S., Kamaloo, A., Paydary, K., *et al* (2016) Riluzole in Augmentation of Fluvoxamine for Moderate to Severe Obsessive Compulsive Disorder: Randomized, Double-blind, Placebo-Controlled Study. *Psychiatry and Clinical Neurosciences*, **70**, 332-341. http://dx.doi.org/10.1111/pcn.12394

Esalatmanesh, S., Abrishami, Z., Zeinoddini, A., *et al* (2016) Minocycline combination therapy with fluvoxamine in moderate-to-severe obsessive–compulsive disorder: A placebo-

controlled, double-blind, randomized trial [In Press]. *Psychiatry and Clinical Neurosciences*. http://dx.doi.org/10.1111/pcn.12430

Feusner, J. D., Kerwin, L., Saxena, S., *et al* (2009) Differential Efficacy of Memantine for Obsessive-Compulsive Disorder vs. Generalized Anxiety Disorder: An Open-Label Trial. *Psychopharmacology Bulletin*, **42**, 81-93. http://www.ncbi.nlm.nih.gov/pubmed/19204653

Figueroa, Y., Rosenberg, D. R., Birmaher, B., *et al* (1998) Combination treatment with clomipramine and selective serotonin reuptake inhibitors for obsessive-compulsive disorder in children and adolescents. *Journal of Child and Adolescent Psychopharmacology*, **8**, 61-67. http://www.ncbi.nlm.nih.gov/pubmed/9639080

Fineberg, N. A. & Gale, T. M. (2005) Evidence-based pharmacotherapy of obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology*, **8**, 107-129. http://dx.doi.org/10.1017/S1461145704004675

Fineberg, N. A., Reghunandanan, S., Brown, A., *et al* (2013) Pharmacotherapy of obsessive-compulsive disorder: Evidence-based treatment and beyond. *Australian and New Zealand Journal of Psychiatry*, **47**, 121-141. http://dx.doi.org/10.1177/0004867412461958

Goodman, W. K., Price, L. H., Rasmussen, S. A., *et al* (1989a) The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Archives of General Psychiatry*, **46**, 1012-1016. http://dx.doi.org/10.1001/archpsyc.1989.01810110054008

Goodman, W. K., Price, L. H., Rasmussen, S. A., *et al* (1989b) The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry*, **46**, 1006-1011. http://dx.doi.org/10.1001/archpsyc.1989.01810110048007

Harrison, A., de la Cruz, L. F., Enander, J., *et al* (2016) Cognitive-behavioral therapy for body dysmorphic disorder: A systematic review and meta-analysis of randomized controlled trials. *Clinical Psychology Review*, **48**, 43-51. http://dx.doi.org/10.1016/j.cpr.2016.05.007

Hollander, E., Friedberg, J., Wasserman, S., *et al* (2003) Venlafaxine in Treatment-Resistant Obsessive-Compulsive Disorder. *Journal of Clinical Psychiatry*, **64**, 546-550. http://www.ncbi.nlm.nih.gov/pubmed/12755657

Howson, A. L., Batth, S., Ilivitsky, V., *et al* (2004) Clinical and attentional effects of acute nicotine treatment in Tourette's syndrome. *European Psychiatry*, **19**, 102-112. http://www.ncbi.nlm.nih.gov/pubmed/15132126

Katzman, M. A., Bleau, P., Blier, P., *et al* (2014) Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*, **14**, S1. http://dx.doi.org/10.1186/1471-244X-14-S1-S1

Komossa, K., Depping, A. M., Meyer, M., *et al* (2010) Second-generation antipsychotics for obsessive compulsive disorder. In *Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD008141. DOI: 10.1002/14651858.CD008141.pub2.* Chichester, UK: John Wiley & Sons, Ltd. http://dx.doi.org/10.1002/14651858.CD008141.pub2

Kushner, M. G., Kim, S. W., Donahue, C., *et al* (2007) D-Cycloserine Augmented Exposure Therapy for Obsessive-Compulsive Disorder. *Biological Psychiatry*, **62**, 835-838. http://dx.doi.org/10.1016/j.biopsych.2006.12.020

Mahgoub, N., Asemota, B. & Alexopoulos, G. S. (2011) The Effect of Riluzole Augmentation in a Patient With Treatment-Resistant Obsessive-Compulsive Disorder, Taking Two Other Glutaminergic Agents. *Journal of Neuropsychiatry and Clinical Neurosciences*, **23**, E24-E25. http:/dx.doi.org/10.1176/appi.neuropsych.23.2.E24

McLean, P. D., Whittal, M. L., Thordarson, D. S., *et al* (2001) Cognitive Versus Behavior Therapy in the Group Treatment of Obsessive-Compulsive Disorder. *Journal of Consulting and Clinical Psychology*, **69**, 205-214. http://dx.doi.org/10.1037/0022-006X.69.2.205

Micali, N., Heyman, I., Perez, M., *et al* (2010) Long-term outcomes of obsessive-compulsive disorder: follow-up of 142 children and adolescents. *British Journal of Psychiatry*, **197**, 128-134. http://dx.doi.org/10.1192/bjp.bp.109.075317

Mowla, A., Khajeian, A. M., Sahraian, A., *et al* (2010) Topiramate Augmentation in Resistant OCD: A Double-Blind Placebo-Controlled Clinical Trial. *CNS Spectrums*, **15**. http://www.ncbi.nlm.nih.gov/pubmed/21632011

National Institute for Health and Care Excellence (2013) *Obsessive-compulsive disorder: Evidence Update September 2013*. London: National Collaborating Centre for Mental Health. http://www.evidence.nhs.uk/evidence-update-47

National Institute for Health and Clinical Excellence (2006) *CG31. Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder*. London: National Collaborating Centre for Mental Health. http://www.nice.org.uk/CG031

NHS Education for Scotland (2015) *The Matrix 2014: A Guide to Delivering Evidence-Based Psychological Therapies in Scotland*. Edinburgh: Scottish Government. http://www.nes.scot.nhs.uk/education-and-training/by-discipline/psychology/the-matrix-%282015%29-a-guide-to-delivering-evidence-based-psychological-therapies-in-scotland/the-matrix-%282015%29-a-guide-to-delivering-evidence-based-psychological-therapies-in-scotland.aspx

Ninan, P. T., Koran, L. M., Kiev, A., *et al* (2006) High-Dose Sertraline Strategy for Nonresponders to Acute Treatment for Obsessive-Compulsive Disorder: A Multicenter Double-Blind Trial. *Journal of Clinical Psychiatry*, **67**, 15-22. http://www.ncbi.nlm.nih.gov/pubmed/16426083

Pallanti, S., Bernardi, S., Antonini, S., *et al* (2009) Ondansetron augmentation in treatment-resistant obsessive-compulsive disorder: a preliminary, single-blind, prospective study. *CNS Drugs*, **23**, 1047-1055. http://dx.doi.org/10.2165/11530240-000000000-00000

Pallanti, S., Quercioli, L., Paiva, R. S., *et al* (1999) Citalopram for treatment-resistant obsessive-compulsive disorder. *European Psychiatry*, **14**, 101-106. http://dx.doi.org/10.1016/S0924-9338(99)80725-1

Pampaloni, I., Sivakumaran, T., Hawley, C., *et al* (2010) High-dose selective serotonin reuptake inhibitors in OCD: a systematic retrospective case notes survey. *Journal of Psychopharmacology*, **24**, 1439-1445. http://dx.doi.org/10.1177/0269881109104850

Phillips, K. A. & Hollander, E. (2008) Treating Body Dysmorphic Disorder with Medication: Evidence, Misconceptions, and a Suggested Approach. *Body image*, **5**, 13-27. http://dx.doi.org/10.1016/j.bodyim.2007.12.003

Poyurovsky, M., Weizman, R., Weizman, A., *et al* (2005) Memantine for Treatment-Resistant OCD. *American Journal of Psychiatry*, **162**, 2191. http://dx.doi.org/10.1176/appi.ajp.162.11.2191-a

Ross, S., Fallon, B. A., Petkova, E., *et al* (2008) Long-Term Follow-Up Study of Patients With Refractory Obsessive-Compulsive Disorder. *Journal of Neuropsychiatry and Clinical Neuroscience*, **20**, 450-457. http://dx.doi.org/10.1176/appi.neuropsych.20.4.450

Saxena, S. (2011) Pharmacotherapy of compulsive hoarding. *Journal of Clinical Psychology*, **67**, 477-484. http://dx.doi.org/10.1002/jclp.20792

Sayyah, M., Sayyah, M., Boostani, H., *et al* (2012) Effects of Aripiprazole Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder (A Double Blind Clinical Trial). *Depression and Anxiety*, **29**, 850-854. http://dx.doi.org/10.1002/da.21996

Simeon, J. G., Thatte, S. & Wiggins, D. (1990) Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. *Psychopharmacology Bulletin*, **26**, 285-290. http://www.ncbi.nlm.nih.gov/pubmed/2274627

Simpson, H. B., Foa, E. B., Liebowitz, M. R., *et al* (2013) Cognitive-Behavioral Therapy vs Risperidone for Augmenting Serotonin Reuptake Inhibitors in Obsessive-Compulsive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. http://dx.doi.org/10.1001/jamapsychiatry.2013.1932

Skapinakis, P., Papatheodorou, T. & Mavreas, V. (2007) Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive–compulsive disorder: A meta-analysis of the randomized controlled trials. *European Neuropsychopharmacology*, **17**, 79-93. http://dx.doi.org/10.1016/j.euroneuro.2006.07.002

Skoog, G. & Skoog, I. (1999) A 40-year follow-up of patients with obsessive-compulsive disorder. *Archives of General Psychiatry*, **56**, 121-127. http://www.ncbi.nlm.nih.gov/pubmed/10025435

Soltani, F., Sayyah, M., Feizy, F., *et al* (2010) A double-blind, placebo-controlled pilot study of ondansetron for patients with obsessive-compulsive disorder. *Human Psychopharmacology: Clinical and Experimental*, **25**, 509-513. http://dx.doi.org/10.1002/hup.1145

Steketee, G., Frost, R. & Bogart, K. (1996) The Yale-Brown Obsessive Compulsive Scale: Interview versus self-report. *Behaviour Research and Therapy*, **34**, 675-684. http://dx.doi.org/10.1016/0005-7967(96)00036-8

Stewart, S. E., Jenike, E. A., Hezel, D. M., *et al* (2010) A Single-Blinded Case-Control Study of Memantine in Severe Obsessive-Compulsive Disorder. *Journal of Clinical Psychopharmacology*, **30**, 34-39. http://dx.doi.org/10.1097/JCP.0b013e3181c856de

Storch, E. A., Murphy, T. K., Goodman, W. K., *et al* (2010) A Preliminary Study of D-Cycloserine Augmentation of Cognitive-Behavioral Therapy in Pediatric Obsessive-Compulsive Disorder. *Biological Psychiatry*, **68**, 1073-1076. http://dx.doi.org/10.1016/j.biopsych.2010.07.015

Torres, A. R., Prince, M. J., Bebbington, P. E., *et al* (2006) Obsessive-Compulsive Disorder: Prevalence, Comorbidity, Impact, and Help-Seeking in the British National Psychiatric Morbidity Survey of 2000. *American Journal of Psychiatry*, **163**, 1978-1985. http://dx.doi.org/10.1176/appi.ajp.163.11.1978

Tükel, R., Polat, A., Özdemir, Ö., *et al* (2002) Comorbid conditions in obsessive-compulsive disorder. *Comprehensive Psychiatry*, **43**, 204-209. http://dx.doi.org/10.1053/comp.2002.32355

van Oppen, P., de Haan, E., van Balkom, A. J., *et al* (1995) Cognitive therapy and exposure in vivo in the treatment of obsessive compulsive disorder. *Behaviour Research and Therapy*, **33**, 379-390. http://www.ncbi.nlm.nih.gov/pubmed/7755525

Veale, D. (2004) Body dysmorphic disorder. *Postgraduate Medical Journal*, **80**, 67-71. http://dx.doi.org/10.1136/pmj.2003.015289

Veale, D., Boocock, A., Gournay, K., *et al* (1996) Body Dysmorphic Disorder: A Survey of Fifty Cases. *British Journal of Psychiatry*, **169**, 196-201. http://dx.doi.org/10.1192/bjp.169.2.196

Welkowitz, L. A., Struening, E. L., Pittman, J., *et al* (2000) Obsessive-Compulsive Disorder and Comorbid Anxiety Problems in a National Anxiety Screening Sample. *Journal of Anxiety Disorders*, **14**, 471-482. http://dx.doi.org/10.1016/S0887-6185(00)00034-7

World Health Organisation (1992) *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*. Geneva: World Health Organisation. http://www.who.int/classifications/icd/en/bluebook.pdf