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ANXIETY DISORDERS (DJ STEIN, SECTION EDITOR)

A 2012 Evidence-Based Algorithm for the Pharmacotherapy for Obsessive-Compulsive Disorder

Dan J. Stein · Nastassja Koen · Naomi Fineberg · Leonardo F. Fontenelle · Hisato Matsunaga · David Osser · H. Blair Simpson

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Abstract There is a need to synthesize the growing body of literature on the pharmacotherapeutic management of patients with obsessive-compulsive disorder for clinicians working at a primary care level. We have aimed to generate a simple, easy-to-follow algorithm for the primary care practitioner. This seven-step algorithm addresses diagnosis of obsessive-compulsive disorder, initiation of pharmacotherapy, monitoring and maintenance treatment, and guidelines for the management of patients who are resistant to initial therapy. In creating this algorithm, we have drawn on the body of published evidence, as well as on expert opinion.

Keywords Obsessive-compulsive disorder · OCD · Pharmacotherapy · Anxiety disorders · Algorithm · Treatment · Evidence-based · Primary care

Introduction

Obsessive-compulsive disorder (OCD) is a prevalent psychiatric disorder, with an approximately 1.6 % lifetime prevalence worldwide [1]. Age at onset of this disorder is bimodal (occurring in childhood and early-adulthood), with males and females being affected equally. There is a growing understanding of the psychobiology of OCD, with evidence that frontostriatal neural circuitry and particular gene variants may contribute to pathogenesis [2–4].

Key diagnostic features of OCD are obsessional thoughts and compulsive behaviors. Both sets of symptoms are repetitive and must be significantly time consuming or cause distress or impairment to meet the *DSM-IV* criteria [5]. Individuals with OCD are also more at risk of developing a number of comorbid disorders, including mood disorders

D. J. Stein (✉) · N. Koen
University of Cape Town Department of Psychiatry,
Groote Schuur Hospital J-2,
Anzio Road, Observatory 7925,
Cape Town, South Africa
e-mail: dan.stein@uct.ac.za

N. Koen
e-mail: nastassja.koen@gmail.com

N. Fineberg
Department of Psychiatry, Queen Elizabeth II Hospital,
Howlands, Welwyn Garden City, Hertfordshire AL7 4HQ,
England, UK
e-mail: naomi.fineberg@btinternet.com

L. F. Fontenelle
Department of Psychiatry, Federal University of Rio de Janeiro,
Rio de Janeiro, Brazil
e-mail: lfontenelle@gmail.com

H. Matsunaga
Department of Neuropsychiatry, Hyogo College of Medicine,
Nishinomiya, Japan
e-mail: hisa1311@hyo-med.ac.jp

D. Osser
Department of Psychiatry, Brockton Veteran's Administration
Medical Center,
940 Belmont Street,
Brockton, MA 02301, USA
e-mail: David.Osser@va.gov

H. B. Simpson
Department of Psychiatry, Columbia University and NYS
Psychiatric Institute,
1051 Riverside Drive,
New York, NY 10032, USA
e-mail: simpson@nyspi.columbia.edu

(eg, major depression), other anxiety disorders, and obsessive-compulsive–related disorders [6], thus necessitating a comprehensive diagnostic assessment and intervention [7–9].

Most patients follow a chronic disease pattern, with waxing and waning symptoms. Thus, OCD is associated with significant functional disability and impairment [10], with only 20 % of sufferers achieving full remission [7]. Notably, there is often a delay from onset of symptoms to sufferers' seeking treatment [11]. This delay may compound the broad range of direct (economic) and indirect (psychological, social, occupational) costs incurred by these patients [10].

There has been a great deal of work on the management of this disorder, including a range of systematic reviews, randomized controlled trials, meta-analyses, and expert consensus guidelines [12, 13–16]. However, varied recommendations, limited user-friendliness, and restricted dissemination have all hampered the implementation of these guidelines at the primary care level [16, 17]. Therefore, there is a need for a simple, reliable guideline to assist busy primary care clinicians in optimizing their care of patients with OCD, and to delineate gaps in current theoretical and clinical knowledge [18].

Methods

A literature review was undertaken to collate recent reviews and meta-analyses of the pharmacotherapy of OCD. In addition, the authors distributed a brief questionnaire to a panel of international experts with diverse and extensive experience in OCD. Questions assessed optimal first-line pharmacotherapy of this disorder (including dose and duration), maintenance treatment, and approaches to the management of partial responders and treatment-refractory patients [19]. This paper presents the outcome of that consensus.

Results

Based on our review of the literature and feedback from the expert panel, a sequential, seven-step algorithm for the pharmacotherapy of OCD in the primary care setting was generated (Fig. 1), starting at initial diagnosis and moving through the major aspects of clinical decision-making and pharmacotherapeutic practice. We have also included an evidence-based discussion of each step of this algorithm.

Discussion

While the current algorithm addresses the pharmacotherapy of OCD, several nonpharmacologic interventions have also been found to be useful. As with all anxiety disorders, psychoeducation is key to optimizing outcome [20]. The first-line psychotherapeutic strategy for patients with OCD should then be individual or group cognitive-behavioral therapy (CBT) consisting of exposure and response prevention. This has shown efficacy in OCD [21] by decreasing the rate of relapse and improving symptomatology [22]. Evidence suggests that an acute trial of 13 to 20 once-weekly sessions [23], each lasting 90 to 120 min, is ideal [24]. Realistically, however, this may not be viable in the busy primary care setting, and an acute trial of 7 to 12 sessions has been recommended [23]. Maintenance therapy may then be continued for 3 to 6 months if there is a favorable response to this initial trial [23].

Although some experts advocate the use of combined pharmacotherapy and psychotherapy, there is only limited evidence supporting this approach as the first step in treatment. While the use of fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) [25–27], and clomipramine, a tricyclic antidepressant that also has strong serotonin reuptake inhibition [28, 29], in combination with CBT has been studied in several randomized controlled trials, data on whether combination therapy is superior to monotherapy are mixed [30•, 31]. As discussed below, it may, however, be useful to combine pharmacotherapy and psychotherapy in patients who do not respond to either modality alone.

There is also an emerging body of work on the use of D-cycloserine, a glutamatergic partial *N*-methyl-*D*-aspartate (NMDA) receptor agonist, to augment psychotherapy in individuals with OCD [32, 33]. However, this work is at an early stage, with inconsistent findings in OCD [34]. Further work is required before its use for treatment-resistant OCD patients may be widely recommended.

Our algorithm focuses on adults with OCD. However, juvenile-onset OCD is also common, with a particularly high prevalence in male children with a first-degree relative with the disorder [35]. The clinical presentation of children with OCD is similar to that of adults, with additional comorbid symptoms of conduct disorder and impulsivity [36, 37]. Nevertheless, the treatment of children and adolescents with OCD is also similar to the interventions used in adult patients (ie, CBT and SSRIs) [38].

Step 1: Diagnosis

There are several factors complicating the diagnosis of OCD in patients presenting to the primary care practitioner. First, there is often a delay between onset of symptoms and presentation to the health care system [11]. This may be because patients are too embarrassed to seek care or because they are unaware of the available resources [39]. In either case, concealment of symptoms may confound the assessment of such patients, and the primary care physician should remember to screen routinely for obsessive-compulsive symptoms. Second, critical symptoms of OCD (ie, obsessions and compulsions) may present in

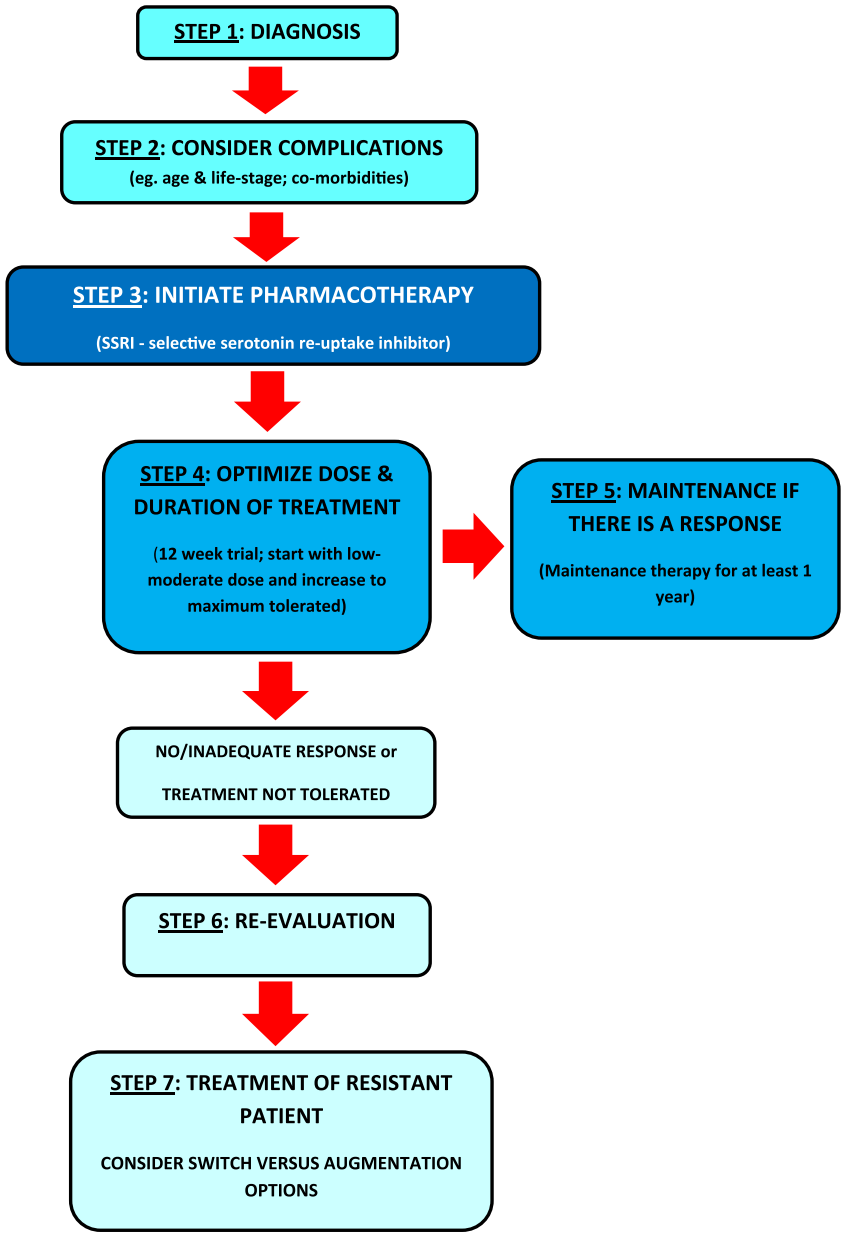

Fig. 1 Algorithm for Pharmacotherapy for Obsessive-Compulsive Disorder (OCD). SSRI – selective serotonin reuptake inhibitor

a remarkably similar way to other conditions, including 1) the delusions of psychotic disorders; the ruminations of major depressive disorder; the preoccupations of generalized anxiety disorder; and the flashbacks of post-traumatic stress disorder, which may emulate OCD obsessions; and 2) the stereotypies and mannerisms seen in psychotic disorders, impulsive acts seen in impulse control disorders, complex tics in Tourette's syndrome, and repetitive behavior and fixed habits in Asperger's syndrome [40]. Third, conditions such as Huntington's disease and poststreptococcal sequelae may also manifest with obsessive-compulsive signs and symptoms. Special investigations (eg, structural brain imaging) may be indicated in selected cases such as late onset of symptoms, atypical presentation, or treatment resistance [39].

It is thus important for the primary care physician to maintain a high index of suspicion and to screen for the symptoms of OCD by using questions for obsessions (eg, "Do you have unpleasant thoughts that keep coming into your mind, even though you don't want them?") and compulsions (eg, "Do you have to do things over and over, even though you don't want to?") [39], or by using a brief, validated screening tool such as the Zohar-Fineberg Obsessive Compulsive Screen. This screen consists of five simple questions and takes less than 1 min to administer [41]. Patients who give a positive response to any of the five questions should then be assessed more fully for OCD. In the primary care setting, practitioners should also routinely perform a comprehensive assessment, including a thorough psychiatric history and examination and general medical inquiry.

Fourth, the primary care physician must remain cognizant of the high rate of comorbidity in OCD [7–9]. Mood disorders (including major depressive disorder with associated suicidality), other anxiety disorders, motor and vocal tics, and a range of obsessive-compulsive spectrum disorders (eg, trichotillomania [recurrent pulling of one's own hair, resulting in hair loss]) [5, 42] are common in patients with OCD and should be evaluated [7–9]. Finally, once a diagnosis of OCD is confirmed, severity should be assessed using a standardized symptom severity scale.

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [43] is a simple, 10-item tool with good psychometric properties that is often used. In this tool, each item is scored on a scale ranging from 0 to 4, with final scores interpreted on a spectrum from subclinical (scores between 0 and 7) to extreme symptoms (32–40). Recently, a dimensional version of the Y-BOCS, which provides severity of different symptom dimensions, was made available [44].

Step 2: Consider Complications

When considering first-line intervention for patients with OCD, it is important to bear in mind a number of potential complications. First, the life stage of the patient may be significant. For example, males frequently display OCD onset in the prepubertal years [45], and there is evidence to suggest an increased vulnerability to OCD in the peri- and postpartum periods (and after miscarriage) [46, 47]. Although extra caution should be exercised when prescribing serotonin reuptake inhibitors (SRIs) to children [48], patients with postpartum OCD may be treated following standard guidelines [49, 50]. However, the potential for adverse events if SSRIs are used during pregnancy—including premature delivery, serotonergic overstimulation, and withdrawal syndromes (eg, hypotonia, respiratory distress, poor feeding) and long-term neurodevelopmental deficits—should also be borne in mind [51]. Furthermore, while older adult patients may be treated following standard guidelines, practitioners should be aware of the risks associated with polypharmacy in these cases. Thus, SSRIs with lower risk of drug–drug interactions (eg, sertraline or escitalopram) should be considered.

The high rate of comorbidity in patients with OCD may also complicate treatment decision-making. For example, patients with comorbid tic disorders should be assessed carefully, as this subset of patients may be more treatment resistant and may require augmentation with dopamine blockers [52–54].

Step 3: Initiate Pharmacotherapy

Evidence supports the use of an SSRI as first-line pharmacotherapy for OCD [12, 13–15]. SSRIs have been found in clinical trials to be effective and safe in treating OCD [55]. Fluoxetine, fluvoxamine, paroxetine, and sertraline have all received US Food and Drug Administration (FDA) approval for treating OCD and may be used in the primary care setting with a degree of confidence. Although there are few head-to-head comparisons of the individual SSRIs, current evidence suggests that there is no significant difference among drugs within the class in terms of efficacy [56]. Nevertheless, there are differences in tolerability among these agents that clinicians should bear in mind.

While gastrointestinal disturbances are the most common adverse effects across the drug class [57], these are often mild and do not affect adherence to and outcome of treatment. More troubling side effects include anxiety, agitation, and insomnia, most often reported with sertraline and fluoxetine use [57, 58]; bleeding complications, the risk of which is significantly increased by concurrent NSAID use [59]; and sexual dysfunction [60]. Weight gain is more common with paroxetine use [61, 62]. Citalopram at high doses (>40 mg/d) has been associated with prolongation of QTc syndrome [63].

The early discovery that clomipramine (CMI) could be used for patients with OCD was important in the development of a serotonin hypothesis of this disorder [64]. In fact, several meta-analyses have suggested that CMI may be more effective than the SSRIs for treating these patients [16]. However, this finding may reflect the lower placebo response rate characterizing these early studies. Many of the more recent head-to-head comparisons have indicated superior tolerability for the SSRIs (with efficacy equal to that of CMI) [65]. CMI may be associated with a host of serious side effects, including seizures, cardiotoxicity, and cognitive impairment, all of which occur less frequently with SSRI use [65]. Like other tricyclic antidepressants, it may cause anticholinergic symptoms and is lethal if taken in overdose. Furthermore, although all SRIs are associated with sexual dysfunction, there is evidence to suggest that individuals using CMI may be more at risk than those using SSRIs [65, 66].

There is very limited literature on the use of other drug classes as first-line monotherapy for patients with OCD. For example, venlafaxine extended release (ER), a serotonin and noradrenaline reuptake inhibitor (SNRI), and clonazepam, a benzodiazepine, have yielded mixed responses in clinical trials [67–71]. Therefore, while several other drug classes have also been studied for the treatment of OCD, none has matched the efficacy and tolerability of the SSRIs. Thus, these agents should be the mainstay of first-line treatment for patients in the primary care setting [12, 13–15].

Step 4: Optimize Dose and Duration

An adequate trial of SSRI therapy for patients with OCD should start at low to moderate dosage (to minimize side effects), and then titrated to the highest dose tolerated. This maximal-dose trial should then be undertaken for at least 6 to 12 weeks, during

Table 1 Recommended SSRI dosage for the treatment of obsessive-compulsive disorder in adults 18–65 years of age

SSRI	Starting dose, *mg/d*	Approved dose, *mg/d*
Fluoxetine	40	20–60
Paroxetine	20	20–40
Sertraline	50	50–200
Citalopram	20	20–40
Escitalopram	10	10–20
Fluvoxamine	50	100–200

SSRI selective serotonin reuptake inhibitor

which time patient response should be monitored [23]. To date, there have been several multiple fixed-dose trials suggesting a positive dose–response relationship for fluoxetine [72, 73], paroxetine [74, 75], and sertraline [76]. A recent meta-analysis also supports the use of dose increase for patients who fail to show a satisfactory response to an initial low dose [77•]. Thus, as a general rule, SSRI dosage should be titrated toward the upper end of the approved range (Table 1).

It is common for psychiatrists to use slightly higher doses than those approved (eg, escitalopram, 30 mg/d). At specialized centers of care, even higher doses are occasionally used [78–80]. However, this approach is not recommended for use in the primary care setting.

It is noteworthy that in 2011, the FDA issued a safety announcement warning against the use of high-dose citalopram (>40 mg/d), due to the risk of dose-dependent QT interval prolongation and torsades de pointes on electrocardiogram [63]. Patients with preexisting congestive cardiac failure, bradyarrhythmias, or predisposition to hypokalemia or hypomagnesemia are at particular risk of developing these cardiac electrical abnormalities and should be closely monitored. In addition, individuals with hepatic impairment, those who are CYP 2 C19 poor metabolizers, or those who are also taking cimetidine are at increased risk, and dosages in these cases should not exceed 20 mg/d [63].

Step 5: Maintenance If There Is a Response

A minority of patients will experience a full resolution of symptoms in response to SSRI treatment of optimal dosage [52, 81]. In these cases, current guidelines suggest that treatment should be continued for at least 1 year, and then gradually discontinued [12, 13, 15]. This is to minimize the risk of relapse, which may be associated with premature discontinuation of SSRI treatment [65]. In the longer term, there is evidence to suggest that select patients can tolerate a gradual dose reduction without worsening of their clinical symptoms [82].

Step 6: Re-evaluation If There Is No Response to Treatment

Most patients treated with an optimal SRI trial will not experience full response to treatment (ie, ≥35 % reduction in Y-BOCS) [19, 52, 81]. Those who fail to achieve full response may be divided into those with a significant improvement in symptoms ("partial responders"; >25 % but <35 % reduction in Y-BOCS) or those with nonresponse (ie, <25 % Y-BOCS reduction) [19].

In the case of nonresponse, it is important to perform a comprehensive reassessment. The initial diagnosis of OCD should be confirmed, as well as any comorbid psychiatric or general medical conditions. In addition, psychosocial factors that may be impairing adherence to medication should be explored. Plasma drug levels may also be checked to assess bioavailability and to rule out ultrarapid metabolism, although the literature supporting this approach is relatively scant [78].

Step 7: Treatment of Resistant Patients

Should a patient remain resistant to treatment with an SRI with continued treatment, options include switching to a different SRI or augmentation. Although the depression literature suggests that one SSRI may work when a prior SSRI trial has failed [83], there are relatively few systematic data on this issue in OCD. Nevertheless, anecdotal experience suggests that this may also hold true in OCD.

Patients who have failed one or more trials of an SSRI may also be switched to CMI, given its somewhat different mechanism of action [84, 85]. While switching to intravenous CMI would bypass hepatic first-pass metabolism, thus addressing the issue of reduced bioavailability, the use of intravenous CMI is not recommended at the primary care level due to the potential for toxicity and the need for specialized monitoring.

In patients with a partial response to an SRI, another option is to move more quickly to augmentation. However, because switching and augmentation strategies have not often been directly compared in OCD, consultation with a psychiatrist may be useful in making such a decision.

Several agents have been studied to augment SSRI therapy. However, the largest body of evidence is in support of low-dose atypical (second-generation) antipsychotics [52] such as risperidone or aripiprazole. While first-generation antipsychotics (eg, haloperidol) showed initial promise as augmentation strategies, their increased side effect profile—including dose-dependent extrapyramidal symptoms—when combined with an SSRI has limited their use [86]. By comparison, the atypical antipsychotics may be better tolerated in short-term efficacy trials, but they have been associated with long-term side effects, including metabolic syndrome [86]. While early data suggested that these agents were specifically appropriate for patients with comorbid tic

disorders [53], it is now generally accepted that they are useful in patients with OCD with and without tics [54, 86]. Importantly, meta-analyses indicate that only about one third to one half of patients will benefit from antipsychotic augmentation [52, 54, 87, 88]. Those patients who do not respond to this augmentation strategy should be removed from the antipsychotic to reduce the risks associated with these medications.

CBT (exposure and response prevention) has also shown efficacy as an augmentation strategy in several open and randomized controlled trials [89, 90], as well as one naturalistic study [91]. At the primary care level, general practitioners should consider the use of this nonpharmacologic intervention before adding less evidence-based medications. If neither antipsychotic nor CBT augmentation is effective, there are some data to support increasing SSRI dosage beyond that which is generally approved [78–80].

Recently, a great deal of work has also been undertaken on the role of the glutamatergic system in the pathogenesis of OCD and on the use of glutamate-modulating agents to augment SSRIs in refractory patients [92]. Such agents include topiramate, an anticonvulsant [93], riluzole [92, 94], and memantine [95], all of which have been shown preliminarily to be useful in treating resistant OCD patients. Further research on these glutamatergic agents is, however, needed.

For persistently refractory cases, there are several other less-supported strategies that may be considered. Such interventions include the use of ondansetron, a 5-HT_3 receptor antagonist [96]; immunoglobulins and plasmapharesis (for specific use in treating pediatric patients) [97–99]; and neurosurgical methods such as deep brain stimulation [100, 101]. However, although these strategies may improve resistant symptoms, their implementation would require referral from the primary level to a more specialized level of care.

Conclusions

With this algorithm, we have attempted to provide a concise, evidence-based, user-friendly tool for use in the primary care setting to manage patients with OCD. This algorithm consists of seven steps, beginning with diagnosis and including initiation of pharmacotherapy, maintenance treatment, and an approach to refractory cases. We have drawn on some of the most widely used current treatment guidelines in conjunction with the views and opinions of a panel of international experts. Thus, it is our hope that this algorithm will contribute to the primary care physician's armamentarium in the treatment of OCD.

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