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Review article

The psychopharmacology algorithm project at the Harvard South Shore Program: An algorithm for adults with obsessive-compulsive disorder

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ABSTRACT

A previous algorithm for the pharmacological treatment of obsessive-compulsive disorder was published in 2012. Developments over the past 7 years suggest an update is needed. The authors conducted searches in PubMed, focusing on new studies and reviews since 2012 that would support or change previous recommendations. We identified exceptions to the main algorithm, including pregnant women and women of child-bearing potential, the elderly, and patients with common medical and psychiatric co-morbidities. Selective serotonin reuptake inhibitors (SSRIs) are still first-line. An adequate trial requires a period at typical antidepressant doses and dose adjustments guided by a plasma level to evaluate for poor adherence or ultra-rapid metabolism. If the response is inadequate, consider a trial of another SSRI this time possibly taken to a very high dose. Clomipramine could be an alternative. If the response to the second trial remains inadequate, the next recommendation is to augment with aripiprazole or risperidone. Alternatively, augmentation with novel agents could be selected, including glutamatergic (memantine, riluzole, topiramate, n-acetylcysteine, lamotrigine), serotonergic (ondansetron), and anti-inflammatory (minocycline, celecoxib) agents. A third option could be transcranial magnetic stimulation. Lastly, after several of these trials, deep brain stimulation and cingulotomy have evidence for a role in the most treatment-refractory patients.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common, chronic neuropsychiatric disorder that causes significant psychosocial impairment (Fineberg et al., 2015). It is characterized by recurrent and persistent obsessions and/or compulsions that the individual feels driven to perform (American Psychiatric Association, 2013). OCD equally affects males and females and has a lifetime prevalence of 1.6% worldwide (Stein et al., 2012). Seeking treatment is often delayed (Stein et al., 2012), and is associated with a poorer outcome, whereas effective pharmacological treatment improves quality of life (Fineberg et al., 2015).

Treatments for OCD include cognitive-behavioral therapy (which may be first-line especially for patients with prominent compulsive behaviors), medication, and their combination (Foa et al., 2005). Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line pharmacological treatment for patients with OCD, but these medications are effective in only 40–60% of patients (Stein et al., 2012). Evidence-informed psychopharmacology algorithms can guide clinicians in choosing appropriate medication options beyond the first-line options for OCD (Burchi et al., 2018). In this article, we present an updated version of a previously published OCD algorithm to which one of the authors (DNO) contributed (Stein et al., 2012).

Since 1995 the Psychopharmacology Algorithm Project at the Harvard South Shore Program (PAPHSS) has been creating evidence-informed treatment algorithms. Eight peer-reviewed PAPHSS algorithms have been published and can also be accessed through a publicly available website (www.psychopharm.mobi).

The PAPHSS algorithms focus on psychopharmacological treatment, but psychotherapeutic and other non-pharmacological treatments for OCD are important. Family counseling or cognitive behavioral therapy incorporating exposure and response prevention could be first-line or integrated with pharmacotherapy at any point (Burchi et al., 2018; Heyman et al., 2006). If and when medication is considered desirable, this algorithm is meant to suggest the best supported and safest options for the first and subsequent medication trials, taking into consideration the common psychiatric and medical comorbidities that might alter the selection process.

2. Methods

The methods used in developing new and revised PAPHSS algorithms have been described previously (Abejuela and Osser, 2016; Ansari and Osser, 2010; Bajor et al., 2011; Giakoumatos and Osser, 2019; Hamoda and Osser, 2008; Mohammad and Osser, 2014; Osser and Dunlop, 2010; Osser et al., 2013).

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In brief, the authors conducted literature searches using PubMed with key words obsessive-compulsive disorder, algorithm, management, and psychopharmacology, focusing on new randomized controlled trials (RCTs), reviews, meta-analyses, and other guidelines published since the last OCD algorithm to which current authors contributed (Stein et al., 2012).

The authors considered efficacy, tolerability, and safety as the main factors for determining the order of recommended pharmacological treatments. All recommendations to retain or change the previously published algorithm were based on the body of evidence reviewed and conclusions agreed upon by the three authors. The peer review process that follows submission of the article also adds validation to the recommendations in this and other PAPHSS algorithms. If the interpretations of the pertinent evidence, and subsequent recommendations, are plausible to reviewers, then they are retained. When differences of opinion occur, the authors make modifications to achieve consensus with the reviewers or examine the relevant evidence further in order to present additional support for their interpretation.

While the algorithm is intended to provide flexible decision-making guidance based on the evidence, clinicians must also consider the unique aspects of each patient's case.

3. Results

3.1. Flow chart for the algorithm

An overview of the algorithm appears in Fig. 1. Each "node" represents a clinical scenario where a treatment choice must be made. The steps in the algorithm progress through initial treatments at the beginning to highly treatment-resistant scenarios at the end. The evidence and reasoning that support the recommendations at each node will be presented below.

3.2. Node 1: Diagnosis of OCD

The treatment recommendations of this algorithm apply only to patients that have been diagnosed with OCD based on the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, edition 5 (DSM-5) criteria (American Psychiatric Association, 1994). These criteria have undergone only very minor changes since the DSM-IV criteria (American Psychiatric Association, 1994) that were in use from 1994 to 2013 when the great majority of psychopharmacology studies of OCD were conducted. The changes mostly clarify previous texts and reorganize where the disorder is found in the manual. It is reasonable to consider the results of studies utilizing the older criteria to apply to patients meeting the present criteria.

Once a diagnosis has been made based on DSM-5 criteria, it is also important to consider any co-occurring psychiatric or medical diagnoses or other circumstances that may be particularly important, such as bipolar disorder and women of childbearing potential. Table 1 provides a brief summary of how these comorbidities and other considerations would modify the basic algorithm.

3.3. Node 2: Start with an SSRI (fluoxetine, fluvoxamine, sertraline)

After making the diagnosis of OCD based on DSM-5 criteria and considering the comorbidities and conditions in Table 1 that might change the basic algorithm, the next step is to initiate a trial of an SSRI (fluoxetine, fluvoxamine, or sertraline) for 8–12 weeks. All three of these options are U.S. Food and Drug Administration (FDA) approved for OCD and are considered first-line. There have been multiple large multi-center studies of each and the details of those studies have been reviewed elsewhere and need not be repeated here (Fineberg and Gale, 2005; Fineberg et al., 2015). However, a few comments pertinent to their first-line selection follow.

Fluoxetine has been found effective in at least some studies at 20, 40, and 60 mg daily at 12–13 week end points, but with greater effectiveness with increasing dose (Tollefson et al., 1994). We will have more to say on this later.

Fluvoxamine (100–300 mg/day) is effective. In one study at a mean dose of 271 mg, 63% of the fluvoxamine CR group versus 46% of the placebo group were responders (defined as a Yale-Brown Obsessive-Compulsive Symptoms score (YBOCS) decrease of ≥ 25%). Fluvoxamine was the first SSRI approved for OCD in the United States. As a result, it is often thought of as a better medication for treating OCD than other SSRIs, but there is no evidence to suggest it is any more effective. Fluvoxamine has significant drug interactions through its inhibition of Cytochrome CYP 1A2, 2C9, C219, and 3A4 metabolizing enzymes that are important to consider (Oesterheld, 1999).

Sertraline was tested in an RCT (50 mg, 100 mg, 200 mg) and all doses were equally effective for OCD symptoms (Greist et al., 1995). In the double-blind phase of a long term 80-week trial ($n = 223$), sertraline was more effective than placebo in preventing: dropout due to relapse or insufficient clinical response (9% versus 24%, respectively) and acute exacerbation of symptoms (12% versus 35%) (Koran et al., 2002). Ninan et al. (2006) studied non-responders after 16 weeks of receiving sertraline 50–200 mg/day. They were randomized to receive an additional 12 weeks of high-dose sertraline (250–400 mg/day) or continue on 200 mg daily. Responder rates (defined as a decrease in YBOCS score of ≥ 25% and a Clinical Global Impression of Improvement (CGI-I) rating ≤ 3) were numerically higher for the high-dose sertraline group versus the 200 mg/day group (52% vs. 34%), although this was not statistically significant (Ninan et al., 2006).

Paroxetine is also FDA-approved for the treatment of OCD but is not recommended as a first-line treatment option due having more side effects than the others. It causes more weight gain (Fava et al., 2000; Uguz et al., 2015), sedation, and constipation (Marks et al., 2008). It also has strong drug-drug interactions due to inhibition at cytochrome P450 2D6. It is particularly prone to produce discontinuation symptoms if stopped abruptly or doses are missed (Marks et al., 2008). Paroxetine is the only SSRI with a category D rating in pregnancy (see Table 1).

Citalopram and escitalopram are not FDA-approved but they are effective for OCD (Montgomery et al., 2001; Stein et al., 2007). Citalopram can cause QTc prolongation with doses of 40 mg and above (Beach et al., 2013), and escitalopram causes moderate dose-dependent QTc prolongation at approved doses (Bird et al., 2014) (see reference 2). Above the maximum dose of 20 mg/day, QTc was prolonged more than the control moxifloxacin. Therefore, we prefer to avoid citalopram and escitalopram because higher doses are often needed.

In summary, the first SSRI trial could be either sertraline, fluoxetine, or fluvoxamine. Unfortunately, SSRIs do have many side effects and these need to be discussed with patients. Perhaps the most disturbing are the sexual side effects and these usually do not diminish over time (Serretti and Chiesa, 2009). Some medical considerations related to these side effects are presented in Table 1.

Considering these side effects, it is recommended to carefully evaluate whether improvement on an SSRI was medication-related and not due to other reasons. As noted above, placebo response rates can be as high as 46%. This can be accomplished by trials off the medication when patients are well and have supports in place.

As noted, some evidence suggests that higher doses (and for a longer time) than usually used for depression may be necessary for maximum results (Bloch et al., 2010; Ninan et al., 2006; Pampaloni et al., 2010). However, over 20 years ago, the Expert Consensus Panel for OCD recommended that patients be treated with moderate doses at first and only increased to high doses after a period of assessment at regular doses (March, 1997). This still seems reasonable. The informative fixed-dose study by Tollefson et al. (1994) showed very little difference in benefit in the first three weeks of treatment with fluoxetine at any dose (20 mg, 40 mg, or 60 mg) or placebo in mean YBOCS total score (Tollefson et al., 1994). At 5 weeks, all the doses start separating from

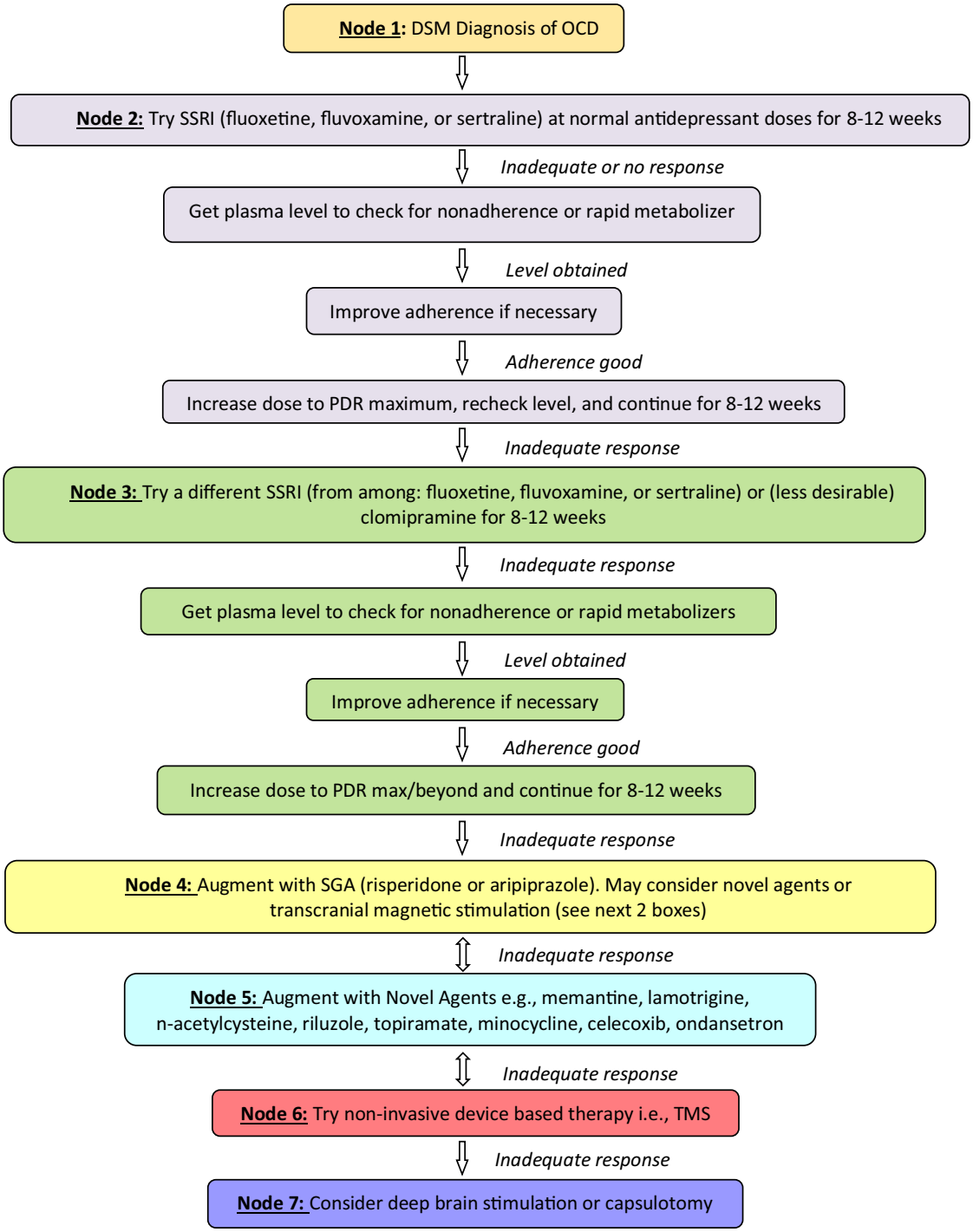

Fig. 1. Flow chart for the algorithm for pharmacotherapy of OCD.

placebo. Then, there appears to be a decision point at about week 7, when the fluoxetine 60 mg dose begins separating slightly from the 40 mg dose. It therefore seems reasonable to recommend that, to minimize unnecessary dose escalation and associated increased side effects, clinicians wait a minimum of 7 weeks before increasing beyond the moderate dose, if the response is inadequate.

There may be three possible outcomes as one proceeds with the moderate dose of the selected SSRI; an adequate response, a partial but inadequate response, or no response. If there is an adequate response, continue with maintenance treatment for at least 1–2 years and then consider tapering to evaluate if the improvement was a placebo effect. Earlier drug discontinuation can be followed by a high likelihood of symptom recurrence (Ravizza et al., 1996). If there is a partial but inadequate response, or no response, the next step is to get a plasma SSRI level to check for nonadherence or rapid metabolizers. This adds "precision medicine" to the case, checking to see if the medication is bioavailable, and it could also help explain problematic side effects (Grunder, 2018). If the plasma level is zero, the patient is most likely non-adherent, so this should be discussed with the patient to see if the problem can be corrected. If adherence appears satisfactory but the plasma level is low, the patient may be a rapid metabolizer of that SSRI. Seven percent of Caucasians and 3% of other ethnicities can be ultra-rapid metabolizers of some SSRIs (Bertilsson et al., 1993). Genetic testing could confirm this. The testing could then indicate which SSRI

Table 1
Comorbidity and other features in obsessive compulsive disorder and how they affect the algorithm.

Comorbidity and other circumstances	Considerations	Recommendations
Cardiac arrhythmias	TCAs may cause cardiac arrhythmias due to their effects on cardiac sodium and potassium channels (Thanacoody and Thomas, 2005).	Try SSRIs before TCAs (clomipramine). EKG monitoring of TCA-treated patients is a more accurate way to detect cardiac toxicity than plasma level monitoring. Sertraline appears to be safe in patients at risk of arrhythmia following myocardial infarction (Glassman et al., 2002). We do not recommend citalopram or escitalopram because of concerns about QTc prolongation (Beach et al., 2013; Bird et al., 2014).
Gastrointestinal bleeding	SSRIs increase hemorrhage risk. Gastrointestinal bleeding can be increased 9-fold by SSRIs combined with NSAIDS (Anglin et al., 2014; Paton and Ferrier, 2005).	Adding proton pump inhibitors such as omeprazole decreases the risk to only slightly above controls not on SSRIs (Paton and Ferrier, 2005).
Older adults (greater than 65 years of age)	SSRIs may increase risk of bleeding; however, in a Cochrane meta-analysis of post-stroke patients, bleeding risk was non-significant (Mead et al., 2013). SSRIs are associated with higher rates of hyponatremia secondary to SIADH in older adults (De Picker et al., 2014). SSRIs, TCAs, and other antidepressant classes have been associated with increased risk of falls, particularly in frail older women (Naples et al., 2016).	Consider side effect profiles of antidepressant medications prior to initiation or titration in elderly adults. In patients with intolerable hyponatremia secondary to SSRI use, consider mirtazapine (De Picker et al., 2014). Escitalopram has fewer drug interactions than fluoxetine or fluvoxamine and less QTc prolongation than citalopram, so it might be considered but QTc should be monitored as the dose goes higher.
Women of child-bearing potential and pregnant women	Severity of OCD is mostly unchanged in pregnancy and postpartum. Predictors of severity of OCD included younger age at delivery and delivery by C-section (House et al., 2016), suggesting that increased surveillance during pregnancy and postpartum may be indicated. There were no differences in neonatal outcomes including birth weight, birth length, estimated gestational age at delivery, or NICU admissions between patients with OCD and those without OCD, and severity of OCD in women who were adequately treated with pharmacotherapy, suggesting that neither disease nor treatment of OCD during pregnancy pose a direct risk to the neonate (House et al., 2016). Alternatively, late exposure to SSRIs (after 20th week of pregnancy) has been associated with increased risk of prematurity, low body weight, neonatal complications (Addis and Koren, 2000) and persistent pulmonary hypertension of the newborn in other studies (Kieler et al., 2012). Some of these could be due to confounding by indication.	The risk to the newborn of maternal treatment may be out-weighed by the impact of uncontrolled OCD symptoms on the patient (House et al., 2016). Avoid paroxetine (D rating due to atrial septal defect risk) (Reefhuis et al., 2015). If the patient is already on paroxetine, consider risks involved with switching. Consider CBT. Treatment choices are a collaborative decision with the patient.
Bipolar disorder	Antidepressants may shift euthymic patients with bipolar disorder toward a manic phase (Sahraian et al., 2017).	CBT and psychoeducation are strongly recommended as a necessary part of treatment. Among antidepressants, tricyclics (clomipramine) should particularly be avoided because of higher mania switch rates (Pacchiarotti et al., 2013). If other antidepressants such as SSRIs are used, they should be added to a mood stabilizer. Even then, their use is associated with a significant increase in [hypo]manic switches on one-year followup (McGirr et al., 2016). Of perhaps greater concern, if the bipolar disorder is rapid cycling, adding an antidepressant triples the rate of recurrent depressions compared with not starting one, according to the STEP-BD study (El-Mallakh et al., 2015). Memantine 20 mg/day showed promise as an effective adjunctive agent in reducing OCD symptoms in manic patients with bipolar I disorder (Sahraian et al., 2017).
Schizophrenia	Obsessive-compulsive symptoms (OCS) occur in the course of many patients with schizophrenia (Schirmbeck et al., 2019) and also can be a new-onset side effect of second generation antipsychotics (SGAs) in these patients, most often with clozapine, due to mechanisms that are unclear (Grillault Laroche and Gaillard, 2016). In addition, some patients with OCD have psychotic symptoms (Cederlof et al., 2015) and such patients may be at risk for developing schizophrenia (Meier et al., 2014). Schizotypal personality, a condition genetically linked to schizophrenia, can present with OCS as well (De Haan, 2015).	CBT and psychoeducation are strongly recommended as a necessary part of treatment if the patient has the capacity to cognitively process and cooperate with the procedures. Use of SSRI antidepressants added to the antipsychotic for these symptoms is reasonable if there is no history of mania (as in schizoaffective disorder). If there is a mania history, review the suggestions for bipolar-related disorders. For treating OCS due to clozapine, first check a plasma level (Meyer, 2019). If it is above usual therapeutic levels, consider lowering the dose to see if the OCS are dose-related and the antipsychotic benefits can be retained. Next, consider treating with sertraline which has the least drug interactions and would be preferred over fluvoxamine (especially), fluoxetine, and paroxetine. When adding an SSRI to other SGAs, other interactions may need to be considered.

would be metabolized normally (Brandl et al., 2014). SSRIs do not have therapeutic levels for treating OCD (Koran et al., 1996) but the laboratory will provide the usual range of levels associated with a given dose.

Once adherence is confirmed, the next step is to increase the dose (if tolerated) to the maximum FDA-recommended dose for OCD (e.g., fluoxetine 80 mg, fluvoxamine 300 mg, or sertraline 200 mg daily) for 8–12 weeks and recheck the plasma SSRI level. A meta-analysis showed that patients obtain only a 9 or 7% greater decline in OCD symptoms on high-dose SSRI compared to low and medium dose SSRI treatment, respectively (Bloch et al., 2010). Therefore, expectations for the results of this increase should be realistic and weighed against any possible

associated additional harms.

Are there other antidepressants that could be considered for initial treatment of OCD?

Bupropion, trazodone, venlafaxine, and duloxetine have received study in OCD but the evidence is not convincing for priority in the algorithm (Balachander et al., 2019; Denys et al., 2003; Phelps and Cates, 2005; Pigott et al., 1992; Sansone and Sansone, 2011; Vulink et al., 2005).

Mirtazapine is a dual neurotransmitter action agent that has the benefit of fewer sexual side effects than SSRIs and SNRIs, and its sedative effects could be useful for anxiety and insomnia. There is one small study of 30 participants who received open-label high-dose mirtazapine 60 mg daily for 12 weeks. It suggested that mirtazapine may be superior to placebo in treating OCD, but the study needs replication (Koran et al., 2005). Of perhaps greater interest regarding mirtazapine, there is a single-blind study of 49 OCD patients (never previously treated) comparing initiating them on citalopram 40–80 mg/day plus mirtazapine 15–30 mg/day versus citalopram plus placebo (Pallanti et al., 2004). Raters were not blind to the treatment group, undermining confidence in the findings, but over the first 4 weeks the results with the combined treatment were significantly better ($p < 0.001$) on YBOC scores. However, by 12 weeks there was no significant difference. It appeared that mirtazapine accelerated the response to the SSRI, though it did not ultimately produce a greater response. Accelerating response would be highly desirable given the discussions above about how long it takes for the SSRIs to achieve their maximum effects. However, it could come at the cost of mirtazapine side effects like weight gain – unless the mirtazapine could be removed after the acceleration and the OCD results maintained. It seems that these findings should be replicated in an appropriately-designed double-blind placebo-controlled study before it should become routine practice to add mirtazapine (Schule and Laakmann, 2005). However, it may be reasonable to explain this option to patients and the evidence behind it, and give it consideration.

3.4. Node 3: Try another SSRI (preferable) or clomipramine

If the patient fails to achieve an adequate improvement on the first SSRI trial, the next recommendation is to try another SSRI from the three first-line options, or consider the tricyclic clomipramine. Clomipramine is effective for OCD and was the first medication approved by the FDA for OCD in the United States (Thoren et al., 1980). Some meta-analyses have concluded that clomipramine has slightly greater efficacy than the SSRIs, but direct comparisons have found no differences (Fineberg and Gale, 2005; Stein et al., 2012). Moreover, early studies with clomipramine may have employed particularly medication-responsive subjects (Fineberg and Gale, 2005). Mostly in Europe, clomipramine has also been used IV to produce a faster response (Koran et al., 1994). Since clomipramine has many more side effects than SSRIs especially seizures, cardiotoxicity, weight gain, anticholinergic effects, particularly strong sexual dysfunction, and overdose lethality, the general preference is to try another SSRI for the second trial. Controlled studies, however, have not been done to evaluate whether patients who failed one adequate SSRI trial would respond to a second SSRI trial versus other medication options like augmentation strategies. The Expert Consensus group estimated a 40% likelihood of a significant response to a second SSRI trial (March, 1997). Notably, other disorders that can be treated with SSRIs such as major depression can respond to a different SSRI after failure on a first (Rush et al., 2006). SSRIs differ somewhat in their neurotransmitter-based activities. Furthermore, the side effects for patients are probably greater when adding the most-studied augmenting medications (second generation antipsychotics), compared with trying a different SSRI.

As in the first SSRI trial, there are three potential outcomes; an adequate response in which the maintenance dose would be continued, a partial but inadequate response, or no response. Again, plasma levels should be checked for nonadherence and rapid metabolizers. Once adherence is confirmed, the dose should then be increased if tolerated, to the maximum recommended dose. However, node 3 differs from node 2 in that if the response is inadequate or there is no response, and the plasma level has been adjusted to typical levels, consideration could be given for pushing the dose of the second SSRI beyond that recommended in the manufacturer's package insert. This suggestion is based on limited evidence. As described earlier, Ninan et al. (2006) found that among acute phase non-responders, continuation treatment with high-dose (250–400 mg) sertraline sometimes gave greater and more rapid improvement in OCD symptoms compared to continuing the maximal-labeled dose of sertraline (200 mg). This suggests that some patients who do not respond with doses up to 200 mg/day of sertraline may benefit from higher doses. However, these patients did not have baseline sertraline plasma levels before the dose increases. In this algorithm, this would have occurred, and dose adjustments made. It is unclear if the benefits seen in Ninan et al. (2006) could occur in patients raised to above normal plasma levels, and it is unclear if the side effect burden would be increased in such cases. However, if typical levels have been well tolerated, it seems reasonable to consider a dose increase as in Ninan et al. (2006). There were, in fact, somewhat higher rates of tremor and agitation seen on the higher doses. In the next step in the algorithm (node 4) the recommendation is to augment with SGAs, which have significant side effect profiles and, often, marginal benefits. Therefore, it may be a safer and possibly effective option for some patients to try an SSRI dose above the FDA maximum.

Other antidepressant options to consider for node 3:

Venlafaxine was mentioned earlier and has evidence of comparable effectiveness to a second SSRI. However, it has more side effects including hypertension especially at high doses, higher overdose lethality risk, and greater gastrointestinal problems (Giakoumatos and Osser, 2019).

3.5. Node 4: Augment the SSRI with a second-generation antipsychotic

If there is no or a partial but inadequate response to the second SSRI, options could include a third SSRI or clomipramine, or an augmentation strategy. The latter have received much more study and there are some positive findings. Among the augmentations, the most evidence has accumulated with SGAs, and, of those, the results favor choosing aripiprazole or risperidone. Antipsychotic augmentation has been associated with significant improvement in approximately one third of patients (Diniz et al., 2011). Other augmentations and treatment strategies are discussed in nodes 5 and 6, and prescribers should look over those options as well before making a decision at this point since they may appear better suited to the individual patient.

Risperidone (0.5 mg/day) and *aripiprazole* (10 mg/day or possibly lower) have the most evidence of short-term benefit (Veale et al., 2014). In this meta-analysis, there were 5 small studies involving low-dose risperidone, with a total of 77 participants receiving risperidone and 89 participants receiving placebo. The risperidone group had a 3.9-point reduction in overall mean YBOCS score, which was statistically significant compared to the placebo. The number needed to treat (NNT) for significant improvement was 4.65. There were 2 aripiprazole trials including a total of 41 participants on aripiprazole and 38 on placebo. There was a 6.3-point improvement on YBOCS outcome scores between the aripiprazole group and placebo, which was statistically and clinically significant. Of note, 50% of participants on the SGAs had a greater than 10% increase in body mass index (BMI) compared to 15.2% with an elevated BMI in the SSRI plus placebo group. The SGA group also had a higher fasting blood sugar. These risks should be taken into consideration and discussed with the patient before choosing an SGA as an augmentation strategy. Notably, the benefits from the augmentation seemed to plateau at 4 weeks and there was no further improvement after that. Therefore, if aripiprazole or risperidone are used for

treatment-resistant OCD, they should be trialed for no longer than 4 weeks (and without other interventions) to determine effectiveness. If a patient is determined to be a responder at 4 weeks, then another discussion should be had regarding the possible long-term risks and need for regular monitoring of weight, blood sugar, and lipid profile.

There is also one single-blind head-to-head comparison of risperidone versus aripiprazole which found a greater response rate for risperidone. Participants were placed on high doses of either sertraline, fluoxetine, or paroxetine for 12 weeks, and those who did not achieve an improvement of ≥35% on the YBOCS were considered refractory and augmented for an additional 8 weeks with aripiprazole 15 mg/day or risperidone 3 mg/day (Selvi et al., 2011). It was found that YBOCS scores for both risperidone and aripiprazole significantly declined over the 8 weeks, but risperidone showed a significantly greater response rate of ≥35% on the YBOCS (72.2%, 13 patients) compared to aripiprazole (50%, 8 patients). However, risperidone has a more severe long-term side effect profile in terms of weight gain, sedation, extrapyramidal effects and problems associated with hyperprolactinemia including amenorrhea and sexual dysfunction (Veale et al., 2014).

Of note, most of these SGA trials only last for 8–12 weeks, but when deciding on a medication regimen, it should be taken into consideration that OCD has a chronic relapsing and remitting pattern. One long-term open-label study did not support the effectiveness of SGA augmentation of SSRIs for treatment-resistant OCD. SSRI non-responders who required atypical antipsychotic augmentation had significantly higher total YBOCS scores both at initial assessment and after one year of treatment (initial assessment = 29.3 ± 9.9, after 1 year = 19.3 ± 6.8) compared to SSRI responders (at initial assessment = 25.8 ± 11.4, after 1 year = 13.7 ± 4.6) (Matsunaga et al., 2009). Moreover, the SSRI + atypical antipsychotic group had significantly more side effects.

Veale et al. (2014) found no evidence for the effectiveness of *quetiapine or olanzapine* (Veale et al., 2014). In one study, quetiapine as an augmentation of an SSRI was actually less effective than placebo (Diniz et al., 2011). Notably, in the same study, clomipramine as an augmenter was not different from adding placebo. Some clinicians report from experience that combining an SSRI and clomipramine is an effective augmentation strategy, but the evidence does not support that impression. *Haloperidol* has some evidence of efficacy as an augmenter; however, it is not recommended due to increased risk of long-term adverse effects with the use of first-generation antipsychotics including tardive dyskinesia (Veale et al., 2014).

3.6. Node 5: Novel agents

If there is still an inadequate response, augmentation with novel agents can be considered. As noted in node 4, they might be preferred over the recommended SGAs if the side effects of the SGAs would be unacceptable.

The benefit from some of these novel agents, including memantine, riluzole, topiramate, n-acetylcysteine, lamotrigine and ketamine, theoretically occurs via modulation of glutamatergic pathways. Of these, *memantine* seems particularly promising based on a small amount of evidence. In one RCT, participants with a YBOCS score of 21 or higher were started on fluvoxamine 100–200 mg/day for 8 weeks, and randomly assigned to also receive memantine 20 mg/day (n = 19) or placebo (n = 19). By the end of the trial 89% of the memantine group compared to 32% of the placebo group achieved remission (YBOCS score ≤ 16) (Ghaleiha et al., 2013). Side effects were not different between the two groups. Another RCT (n = 29) demonstrated that, compare to patients with adjuvant placebo, patients who received adjuvant memantine 5–10 mg/day in addition to standard SSRI or clomipramine medication, improved significantly after 12 weeks and were more likely to achieve a full response (35% or more in Y-BOCS reduction) and show a decline in CGI severity over time. It was also found that adjuvant memantine not only affects overall response rate, but also may accelerate monotherapy response rate with a standard SSRI or clomipramine (Haghighi et al., 2013).

Riluzole is a glutamate-blocking agent approved for the treatment of symptoms of amyotrophic lateral sclerosis. An 8-week RCT (n = 50) investigated adding adjuvant riluzole 50 mg twice daily or placebo to fluvoxamine 200 mg/day in patients with moderate to severe OCD. Thirteen patients in the riluzole group achieved remission (YBOCS score ≤16), versus 5 patients in the placebo group, which was significantly different (Emamzadehfard et al., 2016).

Topiramate 50–400 mg/day (mean dose 177.8 mg/day) is another inhibitor of glutamatergic function that has been studied in OCD. When added as an adjuvant to participants' stable SSRI doses, it was shown to significantly reduce compulsion scores on the YBOCS by 5.38 points (versus 0.6 points in the placebo group), but not obsessions or total YBOCS scores (Berlin et al., 2011). However, 28% of 18 subjects receiving topiramate discontinued due to adverse effects.

N-acetylcysteine (NAC) 2000 mg/day is also a glutamate-inhibiting agent that has been studied as an augmenter. NAC or placebo were added to fluvoxamine 200 mg/day in a 10-week double-blind RCT (n = 22 participants in each group). NAC significantly reduced YBOCS total scores and the obsession subscale compared to the control group (Paydary et al., 2016).

Another trial investigated augmentation with *lamotrigine* 100 mg/day or placebo in 33 subjects with persistent OCD symptoms despite an adequate trial on an SSRI for at least 12 weeks. In this 16-week double-blind placebo-controlled trial, significant improvement was achieved on the YBOCS obsession, compulsion, total scores, as well as CGI scores of the lamotrigine group in comparison to the placebo group at the end of the study (Bruno et al., 2012). Thirty-five percent of the lamotrigine group had a reduction of 35% or greater in YBOCS total score, corresponding to a full response, while none of the patients in the placebo group met response criteria of even 25% improvement in YBOCS total score. Lamotrigine was well-tolerated in this trial. Another 12-week study of lamotrigine by Khalkhali et al. (2016) found that SSRI-resistant patients who received adjuvant lamotrigine 100 mg/day to their SSRI (n = 26) had a significant reduction in obsessive and compulsive symptoms on the YBOCS total score and subscores compared to SSRI + placebo (n = 27) (Khalkhali et al., 2016).

Ketamine infusions (0.5 mg/kg over 40 min) were compared with saline infusions in 15 patients with OCD (Rodriguez et al., 2013). In further support of the proposed importance of glutamate mechanisms in OCD, the ketamine subjects had a significant rapid reduction in obsessions mid-infusion, 230 min post-infusion, and 1-week post-infusion. Fifty percent of the ketamine group (n = 8) met treatment response criteria (≥ 35% reduction in YBOCS score) at 1-week post-infusion versus 0% of the placebo group (n = 7), suggesting ketamine's effects on OCD symptoms can last at least a week (Rodriguez et al., 2013). The most common side effects included increases in blood pressure and pulse, and dissociative symptoms during the ketamine infusion. We mention ketamine because of current interest in this product, but much more research is needed before it should be used routinely for OCD.

Other novel agents may reduce OCD symptoms by different mechanisms. *Ondansetron* is a serotonin-3 receptor antagonist used to treat nausea. Patients with OCD symptoms receiving fluoxetine 20 mg/day were augmented with ondansetron 4 mg/day or placebo in an 8-week trial. Patients treated with ondansetron had significantly lower YBOCS scores at weeks 2 and 8 compared to placebo (Soltani et al., 2010). Another 8-week trial (n = 44) involved augmentation of fluvoxamine 100–200 mg/day with either ondansetron 4 mg twice daily or placebo over 8 weeks. It was found that the ondansetron group showed a significant reduction in YBOCS total score from week 4 and thereafter compared to the placebo, such that at the end of the trial, 14 (64%) patients in the ondansetron group versus 6 (27%) patients in the placebo group achieved remission (YBOCS score ≤16) (Heidari et al., 2014).

Agents that reduce neuroinflammation may also serve as effective

augmenters for patients with OCD. In one 10-week trial of augmentation of fluvoxamine 100–200 mg/day with *minocycline* 100 mg twice daily versus augmentation with placebo ($n = 47$ in each group), it was found that the minocycline group had a significantly lower YBOCS total scores compared to the placebo group at the end of the trial. The minocycline group also achieved higher remission, partial, and complete response rates compared to placebo at the end of the trial. Furthermore, there was a significantly shorter period of time needed in the minocycline group than the placebo group for a partial response to be achieved (Esalatmanesh et al., 2016).

In an 8-week trial investigating the anti-inflammatory agent *celecoxib* as an adjunctive treatment of OCD, 27 patients were placed on fluoxetine 20 mg/day plus celecoxib 200 mg twice daily, and 25 patients were placed on fluoxetine 20 mg/day plus placebo. It was found that patients in the celecoxib group had significantly lower YBOCS scores at the end of the study compared to placebo. Both groups showed a decline in mean YBOCS scores during the trial, but the celecoxib group started to decline sooner (by week 2) versus the placebo group (week 4) (Sayyah et al., 2011).

These experimental agents are placed after the SGAs in this algorithm due to the limited amount of evidence on each agent. However, they do show some positive benefit and one could debate whether they should be offered as a group at node 4. It is reasonable to present these options at the same time as antipsychotics, as most of the novel agents, except for ketamine and maybe topiramate, have fewer side effects compared to SGAs.

3.7. Node 6: Non-invasive device based therapy

If SGAs and any novel agents selected are not effective, the next step to consider is transcranial magnetic stimulation (rTMS). It is also reasonable to offer this treatment option at the same time as the novel agents to patients who might prefer this somatic therapy compared to taking another medication. rTMS has received many studies. A recent meta-analysis evaluated 15 RCTs with sham control as adjunctive treatment for OCD. Most of the trials targeted the dorsolateral prefrontal cortex. Active TMS was found to be significantly more effective than sham, but had questionable clinical meaningfulness due to the small effect size (2.94-point difference on YBOCS between groups) (Trevizol et al., 2016). However, media reports of interesting new data submitted to the FDA by the Brainsway "Deep" TMS System involving a study of 100 patients suggested that 38% responded with 30% reduction of YBOCS scores compared to an 11% response rate on sham. The FDA approved the device in 2018. The procedure is to apply the magnet for 25 min, 5 days a week for 6 weeks. The procedure costs over $10,000. An important additional aspect of the treatment in this study was the provision of a brief session just before each procedure in which patients were asked to think about their obsessions and compulsions. Hence, it was really a study of combined cognitive processing and magnetic stimulation. None of the other 15 RCTs employed this method and it may account for the (as yet unpublished) better results. It is unclear where this costly procedure belongs in the algorithm at this time. More study is needed. Also, nothing is known about what maintenance procedures would be needed to sustain the benefit.

Traditional electroconvulsive therapy could be considered for OCD patients who have severe comorbid depression that has not responded to the antidepressant trials (Hanisch et al., 2009).

3.8. Node 7: Neurosurgery

Finally, *deep brain stimulation (DBS) and ablative surgery* have been shown to be beneficial for severe and intractable OCD, but remain experimental. A meta-analysis of 31 DBS trials showed that YBOCS scores improved 45.1% in patients treated with DBS (Alonso et al., 2015). It was also found that 60% of patients treated with DBS met criteria for response to treatment (defined as a reduction of $\geq$ 35% on YBOCS). DBS responders had a significantly older age at onset of OCD than non-responding patients (responders 17.1 years ± 7.9 vs non-responders 13.7 years ± 6.9) and more frequently reported obsessions and compulsions of sexual/religious content than non-responders (33% of responders compared to 0% of non-responders) (Alonso et al., 2015). Most responding patients also reported significant improvement in quality of life. Severe adverse events were less common with DBS than lesional neurosurgery (Alonso et al., 2015). Of note, the optimal brain region is still being established.

There is one double-blind RCT of radiosurgery (gamma ventral capsulotomy - GVC) of the anterior limb of the internal capsule, for patients with intractable OCD, which showed that 2 out of 8 patients (25%) in the active treatment group reached a response at 12 months (defined as a 35% or greater reduction in YBOCS and "improved" or "much improved" on the CGI-I) compared to 0 out of 8 patients in the sham group. This finding suggests that patients who underwent GVC may have benefited more than those who underwent sham surgery, although the difference was not statistically significant. However, in the open long-term follow-up phase, 3 additional patients in the active treatment group responded at post-GVC month 24, raising the response rate to 62.5% (Lopes et al., 2014). Furthermore, 2 out of 4 patients who received active treatment, after having been in the sham group initially, became responders at post-GVC months 12 and 24. In sum, of the 12 patients who ultimately received GVC, 7 (58.3%) became responders. Review of open-label gamma capsulotomy trials showed response rates of at least 55% in patients with severe refractory OCD (Leveque et al., 2013; Ruck et al., 2008). Capsulotomy is also effective in reducing OCD symptoms at long-term follow-up (mean of 10.9 years after surgery), but has a substantial risk of adverse effects, including problems with executive function, apathy, and disinhibition, particularly in patients who received high doses of radiation or underwent multiple surgical procedures (Ruck et al., 2008).

4. Discussion

This algorithm organizes the evidence systematically for practical clinical application and can serve as a guide for clinicians in the management of OCD. It stresses the importance of adequate trials of SSRIs including adding the benefits of measuring plasma levels at times before going on to less established or more side-effect-prone augmentations or somatic procedures. Nevertheless, the treatment of OCD still has many challenges. There is much to be learned about the pathophysiology, genetics, and neurobiology of OCD that could improve future treatment and algorithms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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