

Current Pharmacological Treatment of Obsessive-Compulsive Disorder

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العلاج الدوائي الحالي لاضطراب الوسواس القهري

سداد جواد التميمي ونهلة فوزي جميل

Abstract

Obsessive-Compulsive Disorder (OCD) has moved from an anxiety disorder to a new distinct group of mental disorders. The pharmacological basis for management of OCD is now better understood, and the guidelines for use of medication have proliferated in the past few years. This article reviews the current recommendations and the basis for the use of medication for the treatment of OCD.

Key words: Obsessive-Compulsive Disorder, drug treatment

Declaration of interest: None

Introduction

Obsessive Compulsive Disorder (OCD) remains one of the most challenging mental disorders to manage in clinical practice. The symptoms of OCD are often detected in other psychiatric disorders, and their management could be equally challenging. OCD affects 2-3% of the population. Indeed, the relationship between various psychiatric disorders and OCD are largely speculative. Individuals with OCD might experience additional diagnoses during the course of their illness starting from early teens, which further complicates the clinical picture as well as the management of the OCD itself and the co-morbid psychiatric disorder. OCD might coexist with organic disorders, autism, tics, affective disorders, schizophrenia, anxiety disorders, and personality disorders. All these factors have contributed to the challenges faced by clinicians in managing OCD using psychological therapies, and most importantly pharmacological treatments. The current review focuses on drug treatment of OCD and Obsessive-Compulsive Related Disorders as defined by the forthcoming International Classification of Diseases, 11th Revision (ICD-11).

Current Classification of OCD

It is essential to have an overview of the forthcoming ICD-11 as OCD and related disorders will be incorporated in Obsessive-Compulsive and Related disorders (OCRD).¹ OCD diagnosis remains largely unchanged focusing on the presence of obsessions and/or compulsions, with a range of affective components and in particular obsessions commonly causing anxiety. OCD

is further qualified according to insight (fair-good, and poor-absent), and with panic attacks.

Body Dysmorphic Disorder (BDD) is classified under OCRD. Although BDD criteria are similar to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), but even if the beliefs are considered delusional by the examining psychiatrist, a diagnosis of Delusional Disorder is not made.

Hypochondriasis is grouped underneath OCRD as well as secondary under anxiety and fear related disorders. Absent insight does not qualify for a diagnosis of a Delusional Disorder similar to BDD.

Other diseases classified under OCRD include Hoarding Disorder, Hair-Pulling Disorder, Excoriation Disorder, and Tourette Syndrome.

Treatment of OCD

Treatment of OCD should not differ from any mental disorder, and there is always a need to measure the severity of symptom and their impact on a person's functioning. Mild to moderate OCD as evident by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS),² of a score 8-23, is initially treated by Exposure and Response Prevention (ERP)³ if available with or without pharmacological treatment.⁴ However, it is not uncommon for patients to prefer pharmacological therapy alone following initial presentation. It is generally accepted that psychodynamic psychotherapy is ineffective in the treatment of OCD.⁵ Combined

treatment of ERP and pharmacotherapy is indicated in all severe cases.

SRI's and OCD

The use of Serotonin Reuptake Inhibitors (SRIs) in the treatment of OCD started with Clomipramine⁶ a potent SRI, which is classified as a Tricyclic Antidepressant (TCA) that clarified the role of serotonin in the neurochemistry of the disease. Clomipramine proved to be superior to other TCAs, Mono Amine Oxidase (MAO) inhibitors, benzodiazepines, and was referred to as anti-obsessional drug. It targets the 5-HT transporter protein, which mediates the uptake of intrasynaptic 5-HT leading to increase of intrasynaptic 5-HT concentrations. Treatment of depression with SRI and Selective Serotonin Reuptake Inhibitors (SSRIs) requires continued availability of Presynaptic 5-HT for maintenance treatment, and in patients receiving an SSRI whose depression is in remission, decreased serotonin

leads to recurrence of the disorder.⁷ Patients with OCD do not experience the latter phenomena, and depletion of serotonin levels in patients recovered by use of an SSRI levels do not experience a relapse probably as a result of post synaptic 5-HT receptor changes following treatment.⁷ It is likely that the latter mechanism also explains the late onset of therapeutic effect in OCD estimated at 12 weeks compared to less than six weeks in cases of depression.⁸

SSRIs are the most commonly used medication in the treatment of OCD because of their benign side effects profile and strong evidence of efficacy.⁹ Their use is now generally accepted in children (aged >7 years)^{10,11,12} as well as adults suffering from OCD. A longer initial period of treatment is required to assess clinical response preferably based on the Y-BOCS⁸ compared to the treatment of depression. Similarly, higher doses are often required to achieve a response in comparison to the treatment of depression.⁸

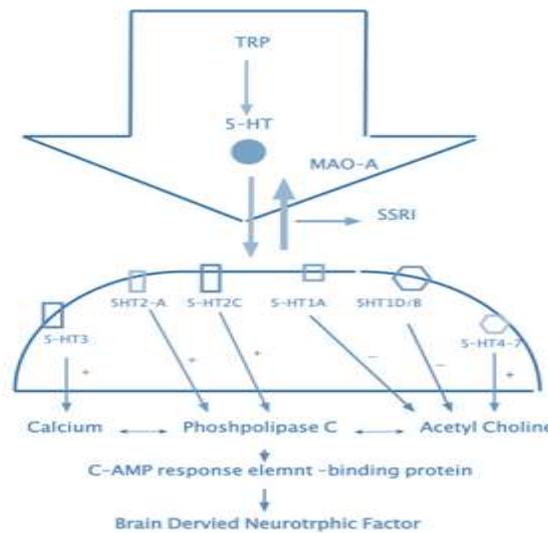


Figure 1. 5-HT reuptake inhibition constitute the main mode of managing OCD. Patients with OCD do not experience disruption of SSRI therapeutic effects under conditions of 5-HT depletion pointing towards long-term postsynaptic 5-HT receptor changes.^{7,8} TRP: Tryptophan. Please refer to text.

Table 1. SRIs in OCD

Drug	Initial dose(mg) daily	Maximum dose(mg)daily
Fluoxetine	20	80
Fluvoxamine	50	300
Sertraline	50	200
Paroxetine	20	60
Citalopram	20	60
Escitalopram	20	40
Clomipramine	25	250

Fluoxetine 20mg daily is the starting dose in adults with increments adjusted by clinical response every two to three weeks up to 60mg daily. Higher doses of 80 and 100mg daily are often reserved to specialist center dealing with severe OCD and should not be attempted in routine outpatient settings.⁹ The relative potency of Fluoxetine for 5-HT reuptake inhibition is less than other SSRIs, and equivalent to Clomipramine, with increased potential of drug- drug interactions. The starting dose for children is 10mg daily with 10mg increments every two to three weeks according to clinical response.

Sertraline^{7,9} has superior relative potency of 5-HT reuptake inhibition, and potentially more rapid improvement of OCD symptomatology, which is probably attributed to its Dopamine (DA) reuptake inhibition. The starting dose is often 50mg daily in adults and 25mg in children with 50mg increments guided by response. The usual daily dose is 100-200mg daily, and higher doses of up to 400mg daily should be reserved for trialingat specialized units for refractory OCD.

Paroxetine possesses a very potent 5-HT reuptake inhibition, and mild DA reuptake inhibition.⁸ The starting dose is 20mg daily with weekly increments of 10mg daily according to response. The drug has anunfavorable reputation because of its discontinuation symptoms and should be avoided in children.

Fluvoxamine¹³ has more potential for drug-drug interactions because it is a potent CYP-3A4 isoenzyme

inhibitor. It is available as immediate - release or extended release preparation and can be used in children. The usual starting dose is 25-50mg daily with 25mg increments every seven days guided by clinical response. The usual daily dose range is 100-300mg daily.

Citalopram has minimal drug-drug interaction potential and is a potent 5-HT reuptake inhibitor.¹⁴ Citalopram is also available as an IV preparation used in refractory cases. The usual starting dose is 20mg daily with increments every two to three weeks of 10mg daily with maximum daily dose of 60mg daily. Escitalopram¹⁵is a more potent enantiomer of Citalopram, and its daily dose is 50% of the dose of its parent drug.

Clomipramine efficacy in treating OCD dates to the 1960s, and it remains the drug of first choice in many centers.⁶ Its relative 5-HT reuptake inhibition is equivalent to Fluoxetine but possess a DA reuptake inhibition effect. It is metabolized to desmethylclomipramine, which is primarily a noradrenaline reuptake blocker. It is cardiotoxic in overdose, and epileptogenic in higher doses especially more than 225mg daily. The usual starting dose is 2mg daily with weekly 25mg daily increments up to 100mg daily. The dose can be titrated upwards after two weeks to a maximum of 250mg daily. It is contraindicated in patients with epilepsy.

Augmentation therapy

Response to SRIs in OCD is often delayed for up to 12 weeks during which the dose of medication is titrated to achieve a therapeutic response with minimal side effects profile.¹⁶ A change of medication might be an option, but augmentation therapy¹⁷ is usually considered after 12 weeks if there is unsatisfactory or partial response to medication. The augmentation strategies could be summarized as follows:

1. Increasing the dose to the maximum tolerable level.¹⁷
2. Clomipramine SSRI combination.¹⁸
3. Intravenous Citalopram.¹⁹
4. Intravenous Clomipramine.²⁰
5. Adding Antipsychotic medication.¹⁷
6. Adding Mirtazapine to an SSRI.²¹

Increasing Fluoxetine to 80-100mg daily should be reserved to management in a specialist center for OCD. Citalopram is notorious for its effect on prolonging the QTc interval, an ECG is required prior to increasing the dose of medication to maximum tolerated level and should be avoided inthe older age group. It is good practice to have a baseline ECG and a measure of QTc interval in all patients with OCD managed with pharmacotherapy.

Intravenous Citalopram¹⁹ 20mg daily titrated up to 40-80mg daily for 21 days followed by Oral Citalopram have shown to be beneficial but should be reserved to management in a specialist center. Similar regime for Clomipramine in dose of 25-250mg daily is used in refractory cases.²⁰

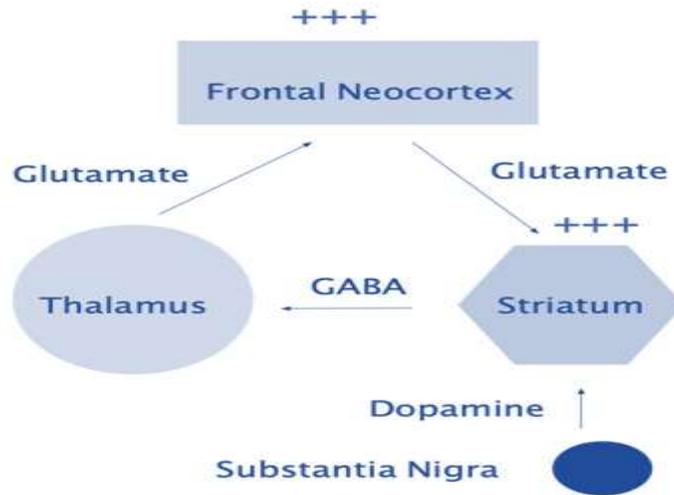


Figure 2. 5-HT modifies glutamate and GABA mediated effects acting on distinct 5-HT receptor subtypes. It is postulated that there is a hyperactivity in the Frontal Neocortex and Striatum in patients with OCD. 5-HT stimulates the release of either Glutamate or GABA. 5-HT₂ receptors were shown to stimulate GABA release and either increase or reduce glutamate release.

Augmentation with antipsychotic medication,¹⁷ is widely used in the treatment of difficult to treat OCD. It is also noted that antipsychotic monotherapy is ineffective in treating OCD and should only be used as adjuvant to SRI. It is hypothesized that 5-HT_{2A} receptor activation antagonize the behaviour aspects of other 5-HT receptor subtypes,²² and atypical antipsychotics as well as Mirtazapine,²⁰ that possess such activity, would function

through antagonism in the medial frontal cortex. It is also postulated that such an effect would be counter-therapeutic with higher doses because of blockade 5-HT_{2A} receptors in orbito-frontal region. There is also evidence of increase dopaminergic activity in the midbrain and basal nuclei, which is compatible with the addiction models of compulsive behaviours.²²

Table 2. Antipsychotic drugs in OCD based on randomized controlled trials

Drug	Initial dose(mg) daily	Maximum dose(mg)daily
Haloperidol	1	5
Quetiapine	25	300
Risperidone	0.5	4
Olanzapine	2.5	10
Aripiprazole	10	30

Haloperidol²³ is a potent D₂ receptor antagonist but has no 5-HT_{2A} receptor antagonism. Atypical antipsychotic¹⁷ listed in Table2 are relatively potent 5-HT_{2A} receptor antagonists as well. Clozapine is ineffective as an add on therapy in OCD probably as a result of 5HT_{1-A} antagonism. Aripiprazole²⁴ is a partial D₂ and 5-HT_{1A} agonist, and it is postulated that the latter mechanism could modulate or reduce SSRI

activation of a feedback mechanism mediated by 5-HT_{1A} receptors which may reduce the firing in 5-HT neurons and attenuated 5HT neurotransmission. Risperidone²³ has been demonstrated to be effective in randomized controlled trials while paliperidone did demonstrate such efficacy.¹⁷ Olanzapine²⁵ is effective as an add- therapy with a dose range of 2.5-10mg daily.

Notes on other medication

There are many drugs referred to in the literature for managing OCD. These notes refer to some of them.

D-cycloserine: May lead to more rapid response to exposure treatment²⁶ although studies have found no difference in treatment outcome with D-cycloserine augmentation in either adult or pediatric patients.

Dextroamphetamine and caffeine: It is postulated that dopamine induced by both drugs may increase D1 receptor stimulation in the pre-frontal cortex, and thus helping to shift attention away from obsessions as well as reducing urges to perform compulsions. Two small double-blind placebo -controlled studies tested the hypothesis and concluded significant improvement in OCD symptoms.²⁷

Memantine: one open label small study demonstrated meaningful improvement in treatment resistant OCD patients treated with memantine, which is a non-competitive glutamate antagonist.²⁸

Ondansetron: anti-obsessional effect involves dopaminergic inhibition by 5-HT3 receptor blockade. It

might be considered as an emerging therapy for augmentation.²⁹

Topiramate: Causes an alteration of the glutamatergic tone³⁰ of the corticostriatal pathway. However, a double-blind, placebo-controlled trial of topiramate augmentation in OCD-resistant patients suggested that it might be beneficial only for compulsions, and not for obsessions.³¹

Riluzole: Causes an alteration of the glutamatergic tone of the corticostriatal pathway. It is still an emerging therapy with no controlled studies.

Venlafaxine: Probably less effective than SSRI in treatment of OCD.³² It is neither a first nor a second choice for treatment of OCD.

Conclusion

The role pharmacotherapy of OCD has become more clarified in recent years, and is probably more distinct from treatment of psychotic, anxiety, and affective disorders.⁵ Pharmacotherapy is often used in conjunction with ERP, but not uncommonly on its own. Treatment of

OCD remains challenging and less than 60% of patients achieve significant remission of symptoms. The review highlights current practice in managing OCD according to guidelines and scientific evidence.

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المخلص

تغير تصنيف اضطراب الوسواس القهري في السنوات الأخيرة وانتقل الى موقع جديد خاص به بعيداً عن اضطرابات القلق والاضطرابات الوجدانية. صاحب ذلك استيعاب أفضل لألية استعمال العقاقير المختلفة في علاج الاضطراب والإرشادات العامة لاستعمالها. هذا المقال يوضح أولاً التصنيف الجديد المرتقب لمنظمة الصحة العالمية لاضطراب الوسواس القهري ، ويتطرق الى التوجيهات العامة لاستعمال العقاقير والخلفية العلمية لاستعمالها.

يتطرقالمقال أولاًللدور بعض مضادات الاكتئاب في علاج الاضطراب وتوضيح التوجيهات العامة.

بعد ذلك يتطرق المقال الى عملية تعزيز العقاقير الأولي مع استعمال عقاقير أخرى. في النهاية يسطر المقال موقع بعض العقاقير الأخرى في العلاج.

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