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Recent Advances in the Pharmacotherapy of Obsessive-compulsive Disorder

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Abstract

Obsessive-Compulsive Disorder (OCD) is one of the most common mental disorders that causes many problems in the occupational and social functioning of the patient. In this review article, we have tried to provide a comprehensive study of various areas of this disease, including pathophysiology, diagnosis, and especially OCD treatment strategies. It seems that the optimal treatment option for this disease is drug therapy, and among these, selective serotonin reuptake inhibitors (SSRIs) are of special importance. However, when the severity of the disease is low or moderate, non-pharmacological strategies such as behavioral therapy and sports intervention therapy may be desirable.

Keywords: Compulsion, Diagnosis, Obsession, SSRIs, Treatment

1. Background

Obsessive-compulsive disorder (OCD) is a set of disturbing thoughts and repetitive actions that are often resulted from anxiety. The OCD patient performs a series of repetitive actions to reduce the annoying thoughts, which in turn can exacerbate the disorder. On the other hand, if the patient resists obsessive action, there is a possibility of increased anxiety. In most cases of this type of disease, the person is aware of the irrationality of the behavior (1). An OCD patient may have only obsessions or compulsions, or both of them. The OCD manifests itself gradually, but this is not a general rule and the disease may appear suddenly (2).

OCD is a disease that can occur with other neurological disorders. Epidemiological estimates indicate that 1 to 3% of people in a community can develop an OCD disorder, and it is most common in people over the age of 20 (3, 4). Among them, 25% of patients recover completely, about 50% have partial recovery, and another 25% remain unchanged or worsen (3). If left untreated, OCD can lead to chronic illness. Various imaging and surgical studies have suggested the association of the orbitofrontal cortex, basal ganglia, anterior cingulate amygdala, and amygdala in the pathophysiology of OCD (5, 6). In general, obsessive-compulsive disorder can be the result of a disturbance in the cortico-striato-thalamic pathway (7-11).

Treatment approaches for OCD include prescribing drugs and behavioral therapy, which in most cases are associated with relapse (12). Reducing anxiety has been effective in improving symptoms Behavioral therapy approaches such as Exposure Response Prevention (EPR) (13) and Acceptance and Commitment Therapy (ACT) (14) methods are recommended for the treatment of patients with mild symptoms. Nevertheless, in many patients with severe OCD, drugs such as selective serotonin reuptake inhibitors (SSRIs) have been prescribed, and the dosage and duration of administration play a central role in improving the condition of patients (15).

Therefore, it seems that using therapies that specifically affect these areas can be beneficial. Therefore, due to the high prevalence of OCD in communities, the study of pharmacotherapy strategies for this disease can be of great importance.

2. Epidemiology

OCD is one of the mental diseases in different societies and its prevalence is 1-3%. This disease manifests itself more chronically and starts mostly at a young age (18-29 years) (16) and the onset of the disease in men is usually earlier than in women and occurs in childhood. Whereas, women usually show this disease more often during adolescence (16). However, the prevalence of this disease is higher in women than in men (17). However, the prevalence of this disease is higher in women than in men (16). Interestingly, only a limited number of them treat this disease and most patients remain untreated (18). The mean prevalence of OCD in Iran is estimated at 1.8%, and women (2.8%) more than men (0.7%) are affected by this disease (19).

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4. Pathophysiology

In the past, the origin of obsessive-compulsive disorder was known only in corticostriatal circuits (20), but recently, with the use of imaging tools, it was cleared that other parts of the brain including the amygdala-cortical circuits, the lateral and medial orbitofrontal cortex (21, 22), the dorsal part of the limbic area, as well as the parietal lobe and forehead, are areas of increased processing of thoughts and actions. Excessive activity in this section causes a lack of control over repetitive activities (23). The association between the limbic network and other areas, including the basal ganglia neural network, varies depending on the degree of disease. Neural connections within the limbic network have been reported to decrease and increase within the Executive/Attention networks, which in turn increases repetitive and disturbing thoughts (24). Neurotransmitters involved in obsessive-compulsive disorder include serotonin, dopamine, and glutamate (25, 26). In a series of neurophysiological studies, changes have been observed in parts of the brain, including the caudate nuclei, the prefrontal dorsolateral cortex, and the modulatory region, in which structural changes occur (27). The location of these changes varies depending on the type of obsessive-compulsive disorder (21). The reduction of the N-acetyl-aspartate (NAA) amino acid in neurons is one of the events that occur in obsessive-compulsive disorder patients. This metabolite has been significantly reduced in other neurological disorders, which increases with the patient's response to treatment (28). On the other hand, according to previous studies vitamin B12, folic acid deficiency, and increased homocysteine play a role in many neurological disorders, these metabolic changes have also been reported in many OCD patients (29, 30).

Genetic and environmental factors can be mentioned as risk factors for OCD. Among the environmental issues, we can mention tensions (31). On the other hand, the patient's attitude towards the disease and the attitude of those around him are very effective in changing the severity of the disease (1). Gender is one of the factors that affect the clinical manifestation of this disorder. Men show obsessive-compulsive symptoms at a younger age than women, and often their obsessive-compulsive disorder is accompanied by unusual sexual behaviors, suspicion, and screening (32). OCD women, on the other hand, are more likely to marry, fear infection, and commit suicide (33). One of the factors that make obsessive-compulsive disorder more severe in women is menstruation (34). This means that many women with obsessive-compulsive disorder first show signs of disease at this time, or that the symptoms of the obsessive-compulsive disorder become more severe at this time (35).

4. Classification of obsessive-compulsive disorder

4.1. Thought obsessions disorder

Thought obsession disorder is a mental occupation with unwanted and annoying thoughts. Fear of illness, infection, danger to others, perfectionism, and harm to loved ones are examples of obsessions (36, 37). Visualization is a type of obsessions that is less common than other types of obsessions (38). In some patients, these disorders occur intermittently, but in other cases, the patient suffers from the disease continuously (39). Different people try different methods to get rid of their annoying thoughts, such as distraction, worry, re-evaluation, and social control. Continuation of these thoughts can lead to compulsions to alleviate the annoying thoughts (40, 41).

4.2. Compulsions

Obsessive-compulsive disorder can lead to forced repetitive actions, including checking, counting, repeating words quietly, storing junk, tidying up, and washing hands to reduce anxiety (42, 43). One of the most common types of obsessive-compulsive disorder (OCD) is washing disorder (44). In this type, the person is afraid of becoming infected with various types of contaminants and transmitting them to other people. The person is terrified of using public toilets, and restaurants, touching the door handle, and shaking hands with others (45). On the other hand, other behaviors such as worrying about an accident for relatives, saying something that upsets loved ones, and reading sentences and writings to worry about their forgetfulness can be symptoms of this obsession (46). Regulators are those who want what is around them to be in a sure orderly, and symmetrical order (47). Some patients collect valuables and are unable to separate them (48).

5. Diagnosis

The diagnosis is usually based on clinical observations. The disease has a wide range of symptoms that affect emotions, cognition, and social communication. In addition, along with these symptoms, several comorbid disorders occur when OCD occurs (49). People with obsessive-compulsive disorder show very similar symptoms to other mental illnesses. In this disease, the patient realizes that his/her behavior is irrational and refuses to declare the troubles (50). But in most cases, the disease is acute and the patient has a poor diagnosis of his condition and considers his actions and thoughts justifiable. The severity of the disease varies from person to person. The patient can often hide this problem from those around them. Therefore, many of these patients refuse treatment (51). In general, the symptoms that exist in a person with obsessive-compulsive disorder include a series of thoughts, mental imagery, and repetitive actions that are distressing the patient, leading to depression and emotional distress. To alleviate this state of mind, the patient begins to replace these thoughts with other thoughts or perform a series of repetitive actions (37). Differences in disease symptoms are the result of genetic heterogeneity in the disease (52). The DSM-5 diagnostic criteria for obsessive-compulsive disorder are listed in Table 1.

Table 1. The DSM-5 diagnostic criteria for obsessive-compulsive disorder (30-32)

I.	Obsessions or compulsions or both of them
II.	OCD should cause a significant disruption in a person's life (in professional and social performance, etc.) and the person should devote more than one hour a day to repetitive actions.
III.	Obsessive-compulsive disorder should not be due to the physiological effects of one substance (drug or drug) or another disease.
IV.	Other psychiatric symptoms should not justify the symptoms.

6. Treatment

There are various treatments for obsessive-compulsive disorder, however, between 25 and 40% of patients receiving conventional therapies do not fully respond to treatment and still show symptoms or relapse (41). On the other hand, most patients with obsessive-compulsive disorder see a doctor or psychologist 5 to 10 years after the first signs of their illness. The use of treatment depends on the severity of the disease and the types of disorders associated with the disease. Reducing anxiety around is one of the therapeutic goals used in therapeutic methods. These treatments have shown different effects for each type of obsession. For example, the treatment method is very effective in treating infections of obsessive-compulsive disorder (53). The treatment process has taken years to show significant results.

6.1. Behavior therapy

Behavior therapy is one of the methods that is done with the help of a psychologist. This treatment is more effective than drug therapy in cases where obsessive-compulsive disorder is not severe (54). Exposure Response Prevention (EPR) is one of the behavioral therapy

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methods in which the patient is exposed to his fears. In this way, the person is asked to touch the objects he is afraid of and to avoid washing (13). On the other hand, some psychologists find this method very difficult and tedious (45) and suggest other methods such as the Acceptance and Commitment Therapy (ACT) method which is based on acceptance and commitment. This method is shown as a part of the third wave of behavioral therapies based on the relational frame theory (RFT) for the effective treatment of many mental disorders. This method allows obsessive thoughts and behaviors to be maneuvered, and any confrontation with the repetition of obsessive behavior is considered ineffective and even worsens the symptoms (14). Another treatment method is the use of self-help techniques that are very effective in improving the symptoms of the disease (55). One of the self-help methods is the use of computer techniques in this field (56). Cognitive-behavioral therapy (CBT) is another method that is as effective in the treatment of obsessive-compulsive disorder as the ACT method and is often used in patients who do not respond to the exposure method. Using the CBT technique, which is called confrontation and prevention of reaction, this method is to calm the patient so that they can better cope with its exhausting conditions (57). The use of behavioral therapy methods, despite their high effects, has problems, including its high cost (58).

One of the treatment approaches for OCD is meditation, which was recently found in a meta-analysis that combining meditation with medication improves the treatment of OCD (59). Recently, the therapeutic approach based on mindfulness in the treatment of OCD has been highly considered, because it changes negative attention in OCD patients towards themselves with positive thoughts (60). In this approach, the OCD patient is taught to understand present-time experiences without personal judgment, which improves the patient's quality of life. Nevertheless, the effectiveness of this technique is in mild OCD patients, and for severe OCD patients, the combination of drug therapy with meditation is recommended (59).

6.2. Pharmacotherapy

Many medications are effective in treating obsessive-compulsive disorder. Medications are effective for a short time. The most commonly used drugs in the treatment of OCD are selective serotonin reuptake inhibitors (SSRIs) (61). These drugs seem to be the best choice for treating obsessive-compulsive disorder. Fluoxetine is one of the drugs that are very effective in treating obsessive-compulsive disorder. This drug can be effective in diseases such as obsession, depression, and anxiety (62). There is another drug called paroxetine that has fewer side effects and is just as effective (41). Clomipramine is more effective than other serotonin reuptake inhibitors but has more side effects (63). Citalopram and sertraline are other types of SRIs (64). Although the use of these drugs is a common treatment for OCD, it has shown positive effects in only half of OCD patients. How the patient responds to the drug depends on the patient's genetic background (14). There is no difference between the effectiveness of SSRIs in treating obsessive-compulsive disorder, however, some patients may respond more effectively to or tolerate SSRIs. The starting dose of SSRIs is similar to the usual starting dose for depression and takes at least 4 weeks to increase the effective dose. Medications used to treat obsessive-compulsive disorder and their dosages are listed in Table 2.

Table 1. Medications used to treat obsessive-compulsive disorder and their dosages(49-56)

Drugs	Initial dose (mg/day)	Target dose (mg/day)	Maximum dose (mg/day)
Fluoxetine	20	20-40	80
Fluvoxamine	50	200	300
Sertraline	50	200	200
Paroxetine	20	40-60	60
Clomipramine	25	100-250	100-250
Citalopram	20	40-60	80
S- Citalopram	10	20	40
Fluoxetine	20	20-40	80

Approximately 40-60% of OCD patients show clinically significant improvement following the administration of the first prescribed drug (SSRIs) (65). Unfortunately, a large percentage of patients with OCD do not respond to the first dose at all or give little response and need more action. About 20% of patients who do not respond to the first SSRI drug will respond to another drug in the same category. In these cases, it is recommended that the first SSRI drug be discontinued and another drug of the same type be prescribed to the patient. If the second SSRI does not respond, clomipramine will be the third choice, which is usually very effective in people who have not responded to SSRIs (66). Combining SSRIs with clomipramine is one of the most effective treatments in patients responding partially to monotherapy. Of course, drug interaction (increasing the risk of serotonin syndrome) in this drug combination should not be overlooked (66). Antipsychotic medications are another treatment option combined with SSRIs and clomipramine that can be effective in patients suffering from tic disorder at the same time (67). Recent findings suggest the effectiveness of the administration of second-generation antipsychotics such as risperidone (2-4 mg/day), olanzapine (10 to 20 mg/day), and quetiapine (200 mg/day) in combination with SSRIs and clomipramine to treat Resistant OCD (68). Based on the results of studies performed so far, it seems that the addition of risperidone was more effective than the addition of olanzapine or quetiapine (67). Pindolol (2-3.5 mg 3 times daily) in combination with SSRIs has been previously suggested in patients responding partially to SSRIs to increase therapeutic effects but has not been recently accepted in the treatment of OCD. Other drugs used to treat OCD include venlafaxine and clonazepam. In addition, studies have used the increase of mirtazapine to SSRIs in refractory cases, and good effects have been observed (69). The algorithm of OCD pharmacotherapy is shown in Figure 1. Since the discovery of antidepressants, a great deal of information has been obtained about their drug interactions. Drug interactions are particularly important for some specific serotonin reuptake inhibitors and duloxetine. These drugs inhibit the metabolism of many drugs by inhibiting various isoenzymes of cytochrome P450 (70). Often these side effects are dose-dependent and their clinical significance is related to factors such as the drugs involved, and the treatment window affected by the presence or absence of active metabolites of the drug. Specific serotonin reuptake inhibitors are potent inhibitors of cytochrome P450 isoenzymes. However, their tendency to bind to different isoenzymes is different. For example, fluoxetine has a high affinity for the 2D6 isoenzyme, but fluvoxamine has a high affinity for the 1A2 isoenzyme (71). The active metabolite of fluoxetine is also a weak inhibitor of the 3A4 isoenzyme. Compared with fluoxetine, sertraline, citalopram, and S-citalopram are associated with fewer drug interactions. Isoenzyme 3A4 contains the highest amount of isoenzymes in the body, so about half of all drugs used are metabolized through this isoenzyme. Fortunately, only two antidepressants, fluvoxamine, and norfluoxetine are potent inhibitors of this isoenzyme (70). Dangerous drug interactions that occur through this metabolic pathway are cardiac toxicity and malignant ventricular arrhythmias that have been reported with terfenadine, astemizole, and cisapride (72). Another significant interaction of antidepressants occurs when fluoxetine is co-administered with triazole benzodiazepines such as triazolam,

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alprazolam, and midazolam. In this case, the dose of triazolam should be reduced by 75% and the dose of alprazolam by 50%. Therefore, SSRIs administration is the first line for treatment of OCD.

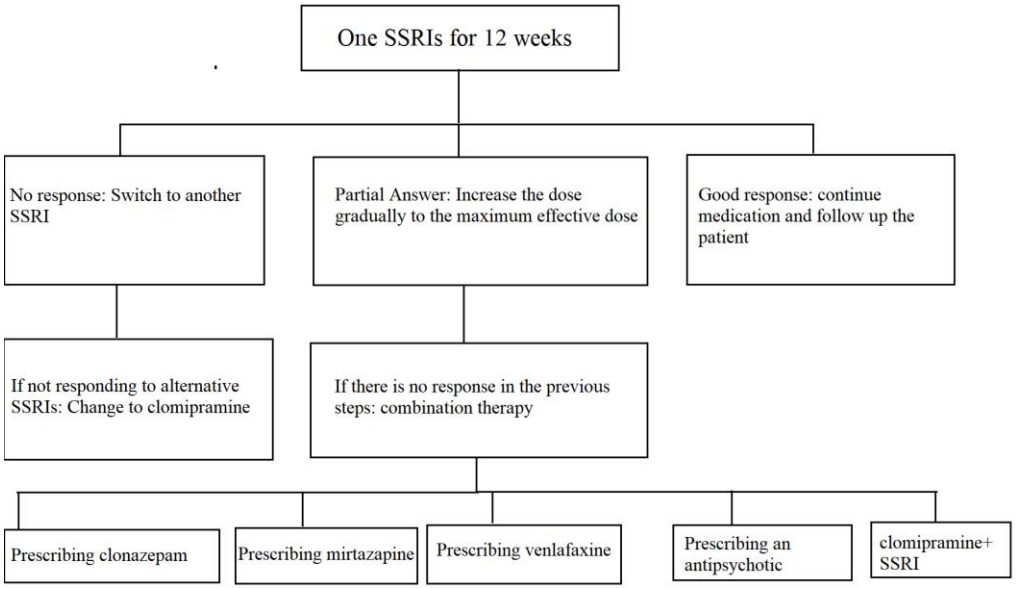

Figure 1. The algorithm of OCD pharmacotherapy. The treatment begins with SSRIs administration. If the patients respond partially to the SSRIs, the dose will increase. In the case of no response to the drug, the drug changes with another SSRIs the follow-up of patients continues. 10.2. Osteogenic and adipogenic differentiation from AM-MSCs

6.3. New treatments for OCD

One of these methods is Repetitive Transcranial Magnetic Stimulation (TMS) (73). This treatment is one of the methods that are effective in treating many behavioral disorders. In this regard, we can mention the use of this method in improving pain, movement disorders, multiple sclerosis, stroke, epilepsy, and various mental disorders. This method is just in the beginning and needs to be optimized. One of the important points in using this method is to use an experienced technician. Because the method of radiation and the dose of treatment are very effective in reducing side effects and increasing the effectiveness of treatment. Surgical methods used in the treatment of obsessive-compulsive disorder include Chronic Electrical Capsular Stimulation, Deep-Brain, Gamma Knife Radio-Surgery (GKRS), Bilateral Anterior Capsulotomy, and Stimulation (74, 75). These methods are used in acute conditions. Another method is Electroconvulsive Therapy (ECT), which is not a common treatment but is used in acute conditions of the disease (76). In general, surgery is used when other treatments are no longer responsive (77). Exercise therapy is another treatment that can be useful along with other methods (78). The types of treatments commonly used to treat obsessive-compulsive disorder are listed in Table 3.

Table 3. A variety of common treatments for obsessive-compulsive disorder

Methods	Type	Action mechanism	Side effect
Behavior therapy	Exposure method (ERP) (71)	Faced with factors that the patient is afraid of (72)	The high cost (46)
	ACT-based on Acceptance and commitment (65) Mindfulness method (ATT) (66)	Increase patient psychological awareness (67)	
	Computer-assisted Self-help(73)	Utilization of computer programs and manuals (74)	
Pharmacotherapy	Fluoxetine (75), fluvoxamine (76), paroxidine (45), citalopram (77), sertraline (72), clomipramine (55), risperidone (78) and dicycloserine (79)	Selective Serotonin reuptake inhibitors (SSRIs) (53)	Headache, Insomnia, Nausea, weakness, Dry mouth, Weight gain, Confusion (80, 81)
Repetitive transcranial magnetic stimulation (rTMS) (77)	Single-pulse paired pulsed and tandem pulses (82)	Creating a magnetic field reduces the excessive activity of the brain (83).	Headache, Nausea (83)
Electroconvulsive therapy (ECT) (84)	One-way ECT (low, medium, and high dose), two-way ECT (85)	Electroconvulsive therapy (increase in GABA neurotransmitter) (86)	Amnesia (87)
Sports intervention therapy (88)	yoga	Increased endorphins (89)	

7. Conclusion

In general, it is concluded that the treatment of OCD patients depends on the severity of the disorder, and in mild cases behavioral therapy and in high severity drug therapy are recommended and if the patient does not respond, antipsychotic drugs should be used.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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